Benzyne in synthesis: A search for palladium catalysed three-component couplings

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Declaration

This thesis was submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Edinburgh. Unless otherwise stated the work described in this thesis is original and has not been submitted previously in whole or in part for any degree or other qualifications at this, or any other university.

Jaclyn Henderson

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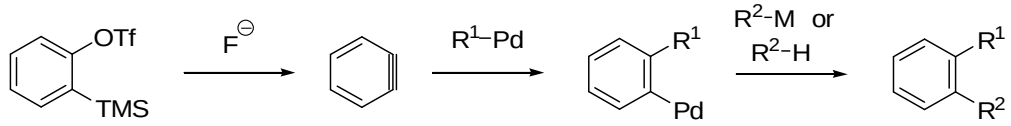
Abstract

It is over 100 years since scientists first postulated the existence of arynes as reactive intermediates. Their use in organic synthesis is now well-established and investigations into novel methods for their generation and utility in carbon-carbon bond forming reactions continue to this day. In 1983 Kobayashi and co-workers introduced a novel method of generating benzyne under mild conditions, using a fluoride induced decomposition of 2-(trimethylsilyl)phenyl triflate **1**. This development has opened the door to employing arynes in a variety of transition-metal mediated carbon-carbon bond forming processes. Intermolecular carbopalladation, in particular, stands out as a powerful methodology for the construction of diverse 1,2-functionalised arenes through multi-component coupling processes. Initial benzyne carbopalladation with an organopalladium species produces the arylpalladium intermediate **3**, which can then undergo a second coupling to any one of the vast numbers of nucleophiles that have been demonstrated to work in palladium cross coupling.



1 **2** **3** **4**

Presented herein are investigations towards the realisation of such methodology. Initial efforts focussed on its application to the Heck reaction, using acryates as the nucleophilic component. The chemistry has been developed to incorporate a variety of organo-halides in order to generate a variety of molecular architectures; the resultant 1,2-substituted diaryls being useful in the synthesis of both natural products and medicinal chemistry targets. Following successful development of the Heck reaction, investigations of other palladium catalysed couplings were also undertaken, in particular the Buchwald reaction. Initial mechanistic studies are also discussed.

List of Abbreviations

General

atm	Atmospheres
cald.	Calculated
δ	Chemical shift
J	Coupling constant
°C	Degree(s) Celsius
d	Doublet (spectral)
e^-	Electron
S_EAr	Electrophilic aromatic substitution
ES	Electrospray ionization
X	Halogen
Hz	Hertz
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
hr	Hour
IR	Infrared
L	Ligand
LUMO	Lowest unoccupied molecular orbital
MS	Mass spectrometry
m/z	Mass to charge ratio
MPLC	Medium pressure liquid chromatography
MHz	Megahertz
m.p.	Melting Point
M	Metal/metalloid
µL	Microlitre
MW	Microwave
mL	Millilitre
mmol	Millimoles
m	Multiplet (spectral)
NHC	N-heterocyclic carbene

NMR	Nuclear magnetic resonance
o/n	Overnight
M+	Parent molecular ion
ppm	Parts per million
PG	Protecting group
q	Quartet (spectral)
rt/RT	Room temperature
sat.	Saturated
SFC	Supercritical fluid chromatography
TLC	Thin Layer Chromatography
3CC	Three component coupling
t	Triplet (spectral)
2CC	Two component coupling
UV	Ultraviolet
cm^{-1}	Wavenumbers

Reagents and Solvents

MeCN	Acetonitrile
$Pd_2Cl_2(\eta^3\text{-}C_3H_5)_2$	Allylpalladium chloride dimer
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium (0)
dppe	Bis(diphenylphosphino)ethane
dppp	Bis(diphenylphosphino)propane
dppb	Bis(diphenylphosphino)butane
dpppent	Bis(diphenylphosphino)pentane
dpphex	Bis(diphenylphosphino)hexane
dppm	Bis(diphenylphosphino)methane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DPEPhos	Bis(2-diphenylphosphinophenyl) ether
Pd(succinimide)	Bromobis(triphenylphosphine)(N-succinimide)palladium (II)

Herrmann-Beller Palladacycle	trans-Di(μ-acetato)-bis[o-(di-*o*-tolylphosphino)benzyl]dipalladium
$PdCl_2(CN)_2$	Dichlorobis(acetonitrile)palladium (II)
$Pd(dppf)Cl_2$	Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II)
$Pd(PPh_3)_2Cl_2$	Dichlorobis(triphenylphosphine)palladium (II)
DCE	Dichloroethane
DCM	Dichloromethane
Et_2O	Diethyl ether
DMA	Dimethylacetamide
DMAD	Dimethyl acetylenedicarboxylate
DME	1,2-Dimethoxyethane
DMAP	Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DMF	*N*,*N*-Dimethylformamide
EDCI	*N*-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide
EtOAc	Ethyl acetate
HMDS	Hexamethyldisilazane
LDA	Lithium diisopropylamine
NBS	N-bromosuccinimide
$PdCl_2$	Palladium chloride
$Pd(OAc)_2$	Palladium acetate
$Pd(TFA)_2$	Palladium trifluoroacetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium (0)
TBAF	Tetrabutylammonium fluoride
TBAST	Tetrabutylammonium triphenyl difluorosilicate
THF	Tetrahydrofuran
TDMPP	Tris(2,6-dimethoxyphenyl)phosphine
$P(Cy)_3$	Tricyclohexylphosphine
TFA	Trifluoroacetic acid
Triflic acid	Trifluoromethanesulfonic acid
$P(fur)_3$	Tri(2-furyl)phosphine

PEPPSI	(1,3-Bis(2,6-diisopropylphenyl)imidazolidene) (3-chloropyridyl) palladium(II) dichloride
$P(Bu)_3$	Tri-*n*-butylphosphine
$P(tBu)_3.HBF_4$	Tri-*tert*-butylphosphine tetrafluoroborate salt
$P(o\text{-tol})_3$	Tri-*ortho*-tolylphosphine
PPh_3	Triphenylphosphine
XANTPHOS	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Substituents and protecting groups

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
n-Bu	*neo*-Butyl
t-Bu	*tert*-Butyl
Et	Ethyl
M	Metal/metalloid
Mes	Mesityl
Me	Methyl
Ph	Phenyl
i-Pr	*iso*-Propyl
Piv	Pivaloyl
Tf	Trifluoromethanesulfonate
TMS	Trimethylsilyl
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl

Contents

1 Introduction

1.1 Functionalising Aromatic Rings

Aromatic systems are ubiquitous in nature, from the heteroaryl systems found in DNA bases, through to aromatic amino acids and vitamins, along with many natural products (Figure 1.1). They are also found in every area of modern technology – from light emitting diodes, liquid crystalline displays and polymers, through to the latest pharmaceuticals and agrochemicals. Their structural simplicity often masks their preparative complexity and thus efforts towards novel, efficient and convergent syntheses have captured the attention of the synthetic community for more than a century.[1-3]

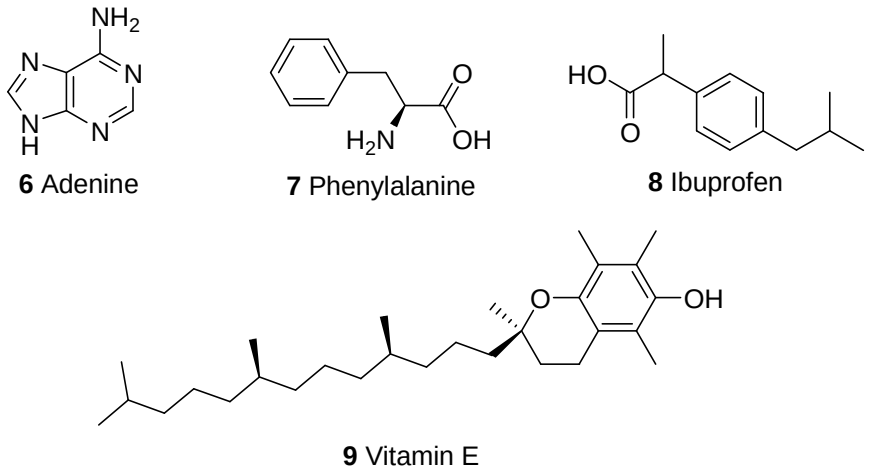


Figure 1.1 Aromatics systems found in a range of materials

Amongst the diverse methods available for functionalising aromatic rings, palladium catalysed reactions have come to the forefront over the last few decades, as they present a versatile toolbox for the construction of a diverse range of aryl bonds in a highly efficient and selective manner.[4, 5]

Aryne chemistry is in the midst of a renaissance, with the last 10 years seeing a vast increase in the publication rate.[6-8] In particular, electrophilic coupling reactions have attracted considerable attention as potent synthetic approaches to substituted

aromatics. Little work has been done on the use of arynes as substrates for palladium catalysed coupling reactions – an approach which could provide an exciting opportunity for the generation of novel polysubstituted aromatics.

1.1.1 Palladium Catalysis

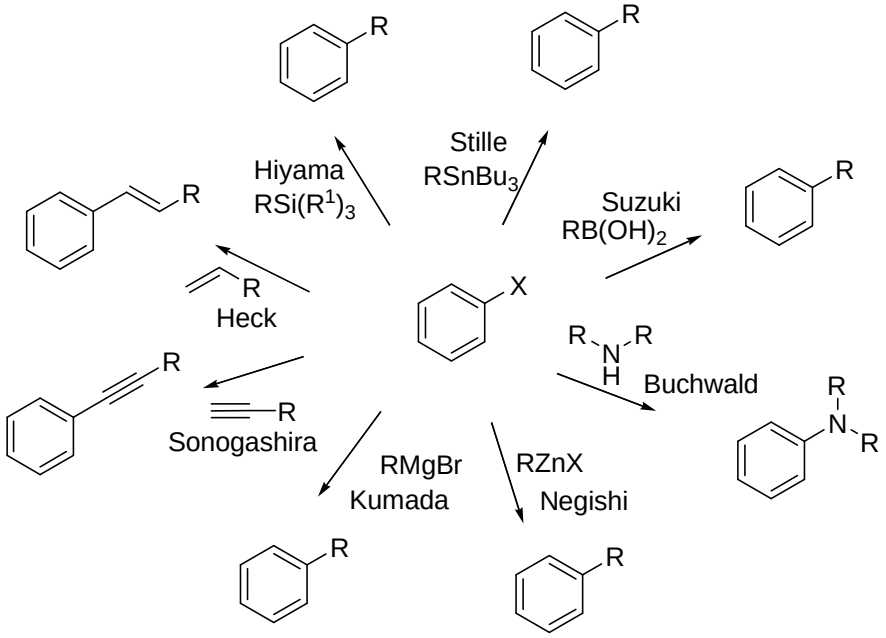


Figure 1.2 Palladium catalysed coupling reactions

Palladium catalysed reactions were introduced as a novel way of forming carbon-carbon bonds in the 1960s and there has since been much research into the development of improved conditions and novel reactions.[9] They also provide a useful tool for the formation of carbon-nitrogen, -oxygen and -sulfur bonds, amongst others (Figure 1.2). In general palladium catalysed carbon-carbon bond forming reactions utilise an organohalide or triflate and an organometallic starting material, undergoing respectively oxidative addition and transmetallation to the palladium species, before reductive elimination to give the new bond whilst regenerating the palladium catalyst (Figure 1.3). The reactivity of the palladium species can be altered by using different ligands, normally phosphine based, but increasingly incorporating nitrogen or N-heterocyclic carbenes (NHC), which allows a wide array of unreactive or sterically hindered precursors to be used. A range of metals are suitable for the transmetallation step from stannanes, employed in the Stille reaction,

through Grignard reagents (Kumada) to boronic acids (Suzuki) and silanes (Hiyama). The field has become so vast, although it has been around for less than half a century, that many texts have been written dealing with the subject.[4, 5, 9]

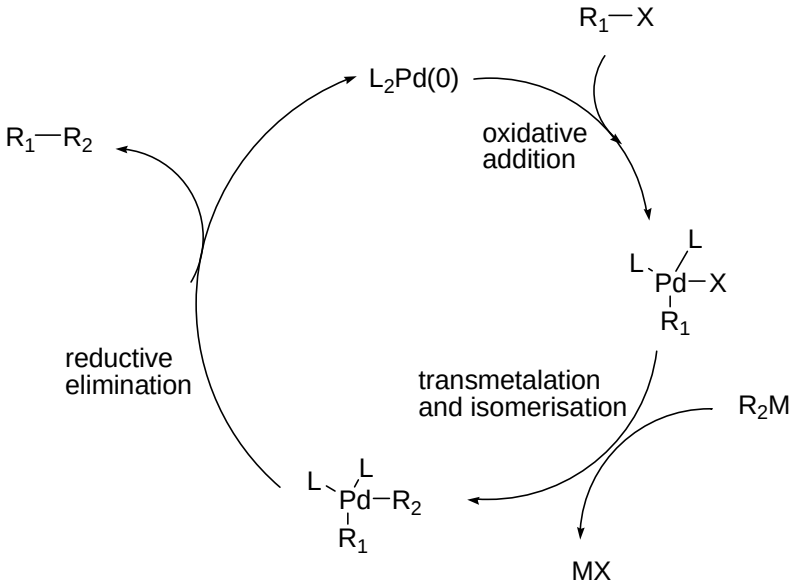


Figure 1.3 Basic mechanism for palladium catalysed reactions

Palladium catalysis has advanced in a spectacular manner, allowing transformations to be performed today which would have previously been impossible. Palladium catalysed cross-couplings have found wide use as key steps in the synthesis of drug molecules, being particularly suitable for combinatorial or parallel approaches. In process development and manufacture palladium catalysis allows for the investigation of economically sound and environmentally friendly methods of synthesis in a shorter period of time, with many drugs on the market featuring a cross-coupling reaction as a key step in their synthesis.[10]

1.1.2 Palladium catalysed direct arylation

Despite the variety of coupling partners in palladium mediated couplings, wide-ranging substrate compatibility and range of mild conditions that can be employed, work continues towards the discovery of new reactions, development of milder and more efficient reaction conditions and further broadening of the reaction scope. In

order to improve further on the conventional palladium catalysed reactions, recent research has sought to remove the need for one of the two functional handles (Figure 1.4). By replacing either the aryl halide or aryl metallic species with an unfunctionalised aromatic, the reactions become more atom economic, and may lose the need for the use of stoichiometric metals or metalloids. Depending on the molecular complexity desired, the functionalised arene precursors required for cross-coupling can be difficult to generate, requiring a number of synthetic steps, may be difficult to handle and are often unstable. A number of terms have been coined including C-H activation, C-H functionalisation, and direct arylation, and several excellent reviews have been written on this highly innovative and exciting area.[11-14]

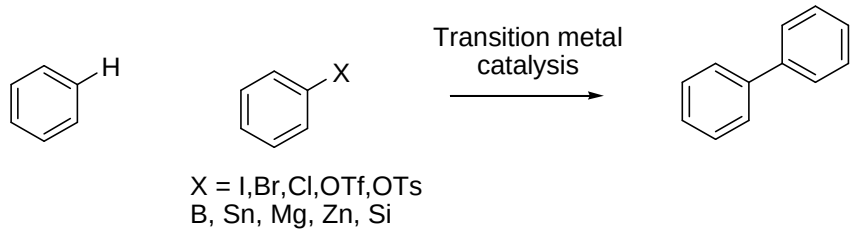


Figure 1.4 Example of direct arylation

Immediately some problems with this approach become apparent: the first is how to activate the normally inert C-H bond so it will undergo oxidative addition or transmetallation when treated with a palladium catalyst. The second is that having achieved a method for palladium insertion, can it be employed regioselectively in complex organic molecules that contain many and varied C-H bonds. Initial successes in this field are found in the functionalisation of heteroaromatics, where the inherent electronic bias of the heterocycle itself influences the regiochemical outcome. π-Electron rich heteroaromatics provide a suitable replacement for the organometallic species, which is typically thought to react as a nucleophile. The heteroatom may also act as a directing group to provide increases in regioselectivity, although additives can sometimes be used to modify the regiochemical outcome. Since the first examples of these reactions were reported in the late 1980's,[15] there have been numerous couplings performed using a wide variety of heteroaromatic systems, with many more advances anticipated (Figure 1.5).

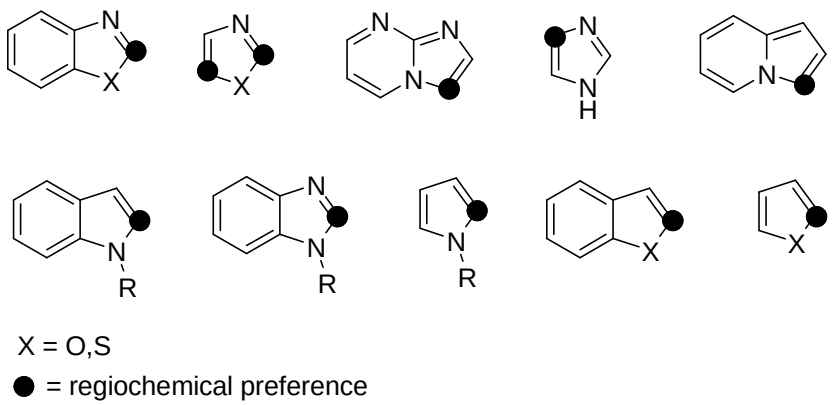


Figure 1.5 Examples of heteroaromatic compounds used in direct arylation, with reaction sites marked

Direct arylations have also been successful with aromatic systems when conducted intramolecularly. A tether reduces the degrees of freedom of the system, thereby controlling the regioselectivity. In the early 1980's, Ames reported his seminal study in this area, demonstrating the formation of complex polycylic systems through intramolecular direct arylation.[16] High yielding reactions could only be achieved where a 5-membered ring was formed; however more recent studies using modern ligand systems have overcome this limitation (Figure 1.6).[14, 17] Several problems are associated with intramolecular direct arylations, namely high catalyst loading, elevated temperatures and hydrodehalogenation producing unwanted by-products.

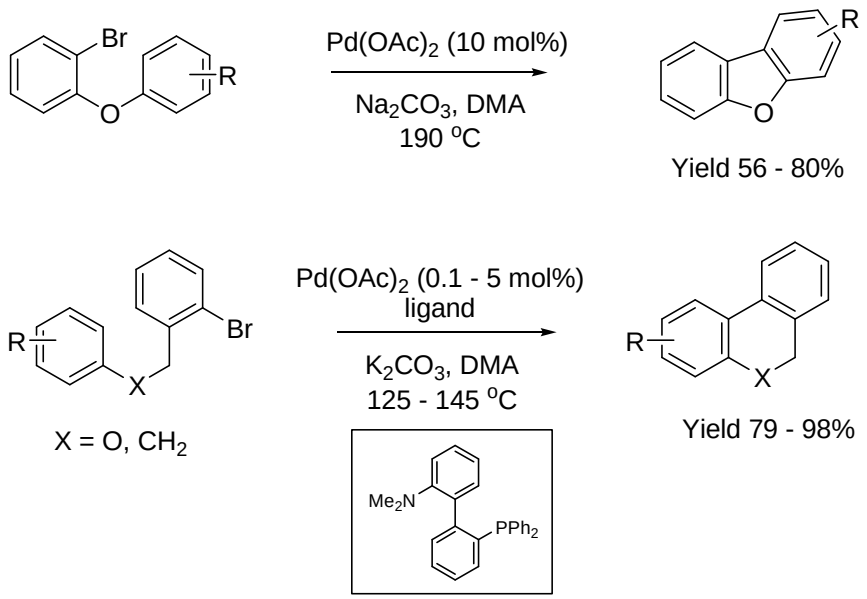


Figure 1.6 Two examples of intramolecular direct arylation.

A number of procedures for establishing regiochemical control for the intermolecular direct arylation of simple arenes have been recently published. Two main factors have been employed to influence the regiochemical outcome of intermolecular direct arylations; the electronics of the aromatic system (for example a reaction will occur *ortho* or *para* to a electron donating group via an electrophilic aromatic substitution (S_EAr) process) or more commonly through the use of a directing group.

Typically directing group assisted reactions employ oxygen or nitrogen containing functional groups; phenol, ketone, amide, imine and pyridine all have been employed with varying levels of success (Figure 1.7). As the interactions between aromatic double bonds and transition metals are typically weak, in comparison to an alkene for example, these directing groups facilitate the arylation step by holding the arene in the coordination sphere of the metal centre. Formation of a 5- or 6-membered metallocycle gives regioselective *ortho* substitution; the selectivity between unsymmetrical *ortho* positions is governed by steric effects.

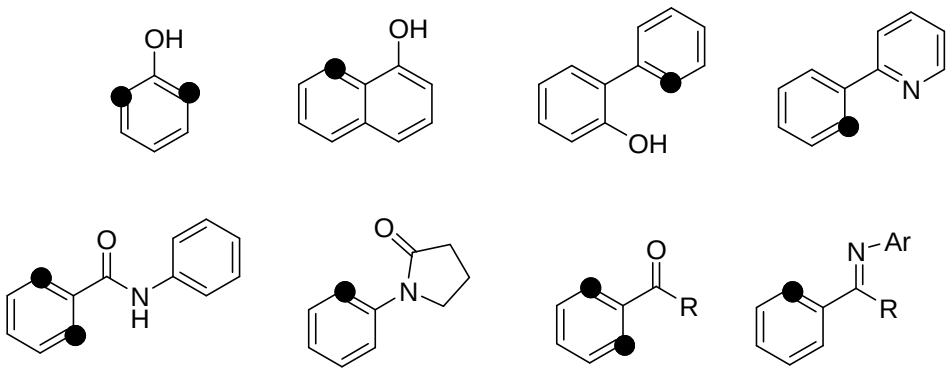


Figure 1.7 Examples of some directing groups used in arylation reactions, with reaction sites marked

One problem with this technique is that mixtures of mono- and di-arylated products are often formed as the propensity of the molecule to undergo further arylation is not significantly altered after the first reaction. In some cases it has been found that using different catalyst systems or changing the aryl halide substrate can affect the reactions selectivity. For example, simple electron rich and electron deficient arenes can be efficiently arylated in the presence of $Pd(OAc)_2$ and an N-heterocyclic carbene (NHC) ligand.[18] The authors found that over arylation could be controlled by changing from aryl bromides to aryl chlorides, therefore attaining selectivity for either mono- or di-arylation (Figure 1.8).

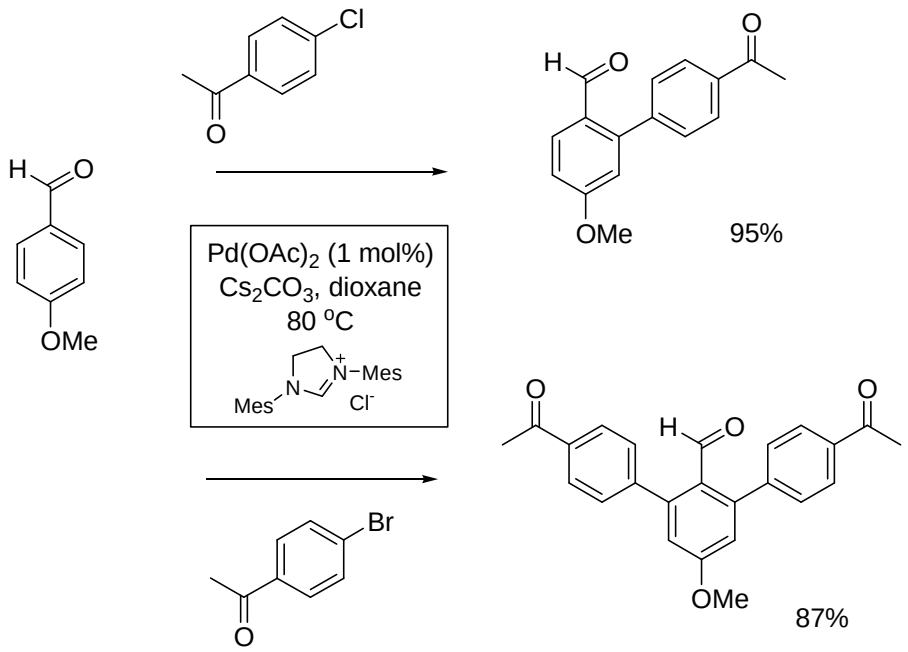


Figure 1.8 Switching selectivity from mono- to diarylation by changing aryl halide

An alternative approach has been taken by Sanford and coworkers, who have reported a palladium catalysed oxidative C-H activation.[19] This highly practical reaction, using hypervalent iodine compounds as the oxidising arylation reagent, doesn't require strong bases or expensive ligands and can be conducted without the necessity to exclude air or moisture. Pyridine and amide directing groups have been used, yielding mono-arylated products from a variety of electron deficient and electron rich precursors (Figure 1.9). Interestingly the reaction can also be used for the arylation of sp^3 hybridised C-H bonds. The only drawback to this method is the requirement for a hypervalent iodine reagent to be used, PhI or PhOTf being unsuitable partners for this coupling. Therefore, one aryl group is sacrificed as PhI during the reaction. The authors have found that selective transfer from a mixed hypervalent iodine reagent can be achieved using [MesIAr]-BF_4; the potentially more precious aryl group is transferred selectively, with the bulky mesityl group acting as a dummy ligand.

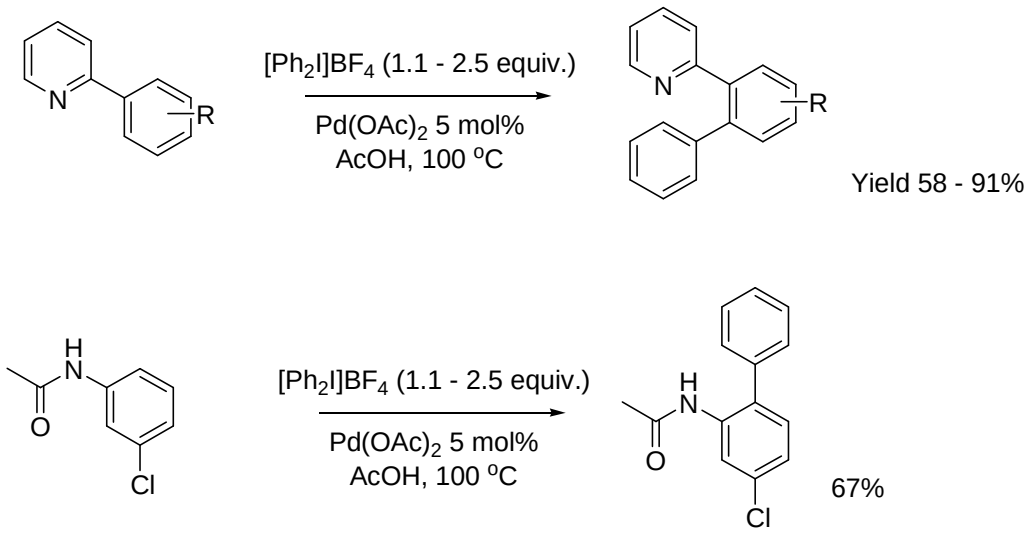


Figure 1.9 Oxidative C-H activation using pyridine or amide directing groups

As well as using palladium as a catalyst in these reactions, ruthenium is also being investigated, yielding some significant successes in couplings with either aryl halide or organometallic substrates. Although the use of ruthenium as an alternative to palladium does not give any significant improvement in cost, handling or reaction conditions, it does increase the range of substrates that can be employed in direct arylations. There has been an even wider range of directing groups utilised for ruthenium catalysed reactions, in particular a range of nitrogen containing heterocycles have been explored.

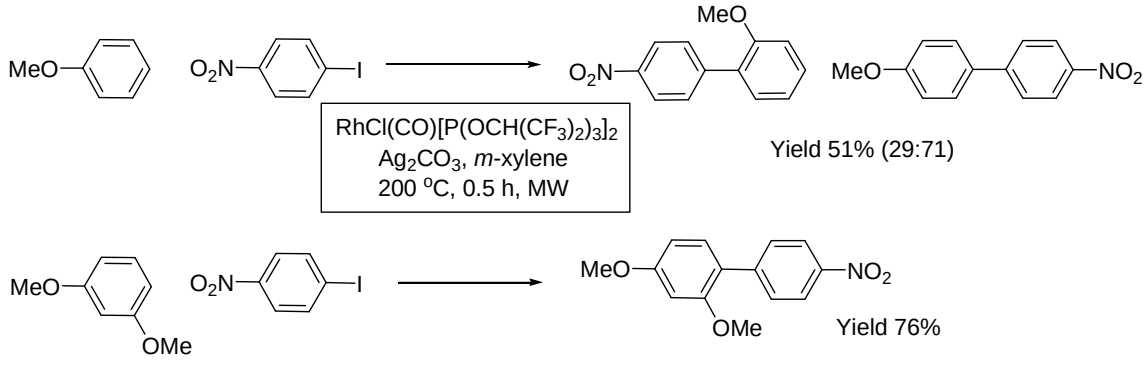


Figure 1.10 Direct arylation through an S_EAr process

Arylation in the absence of directing groups has been a far more demanding challenge, however there have been recent advances in this area. Two are of particular note: during investigation of heteroaromatic direct arylation, Itami and coworkers observed that their system was also efficient for the reaction of electron rich arenes with aryl iodides.[20] The reactions are catalysed by a rhodium complex bearing strongly π-accepting phosphite ligands and proceed through an electrophilic metallation mechanism (S_EAr), as supported by the *ortho-para* selectivity of the reactions (Figure 1.10). In contrast, Fagnou has developed a process for the direct arylation of unfunctionalised aromatics using a palladium-pivalic acid co-catalyst combination (Figure 1.11).[21, 22] The reaction is believed to involve a proton-abstraction mechanism, in which the reactivity depends on C-H acidity rather than the nucleophilicity of the arene. This allows substrates, such as poly-fluorinated arenes, that would be incompatible with other reaction mechanisms to undergo direct arylation with aryl bromides. Yields are good and there have been no reports of the formation of multi-arylated products, however a significant excess of the arene substrate is required.

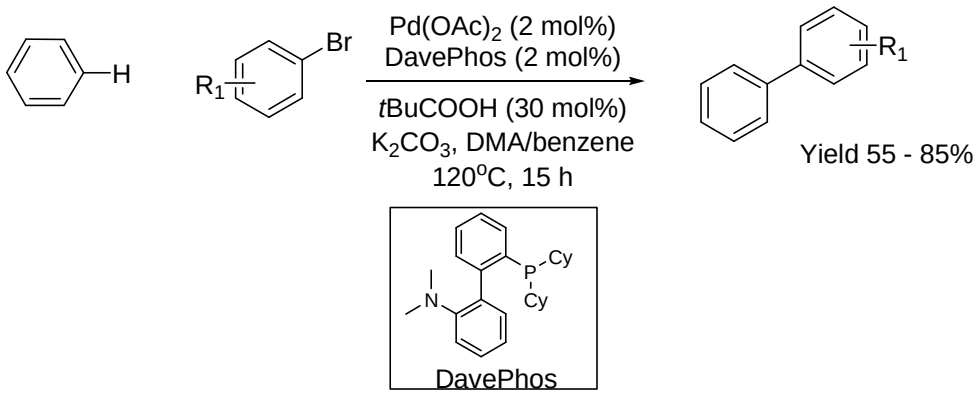


Figure 1.11 Direct arylation via a proton abstraction mechanism

Direct arylation as part of a multi-component reaction sequence is also being investigated, using norbornene as a shuttle for the palladium species. Catellani *et. al.* pioneered this work, uniting an aryl iodide, aryl bromide and alkene to give a net Heck reaction and C-H insertion (Figure 1.12).[23] Selectivity can be achieved by changing the electronic properties of the aryl iodide and aryl bromide, altering their

reactivity. An aryl iodide was chosen that contained an *ortho*-electron donating group that both blocks this position for a second C-H insertion and lowers the rate of reaction of this component with the palladacycle **13**. Concurrent use of an aryl bromide featuring an electron withdrawing group confers additional reactivity towards the palladacycle (Pd(II)) whilst the bromide reacts slower than the iodide with the initial palladium(0) species. The reaction was initially developed with primary alkyl halides, as selectivity for oxidative addition of the aryl iodide *vs* alkyl halide is easier to achieve.[24] C-H activation occurs after oxidative addition and carbopalladation of norbornene through an intramolecular electrophilic aromatic metallation mechanism (S_EAr). Norbornene then undergoes elimination, perhaps promoted by steric bulk, allowing reaction of the aryl palladium species with acrylate in the terminal Heck reaction.

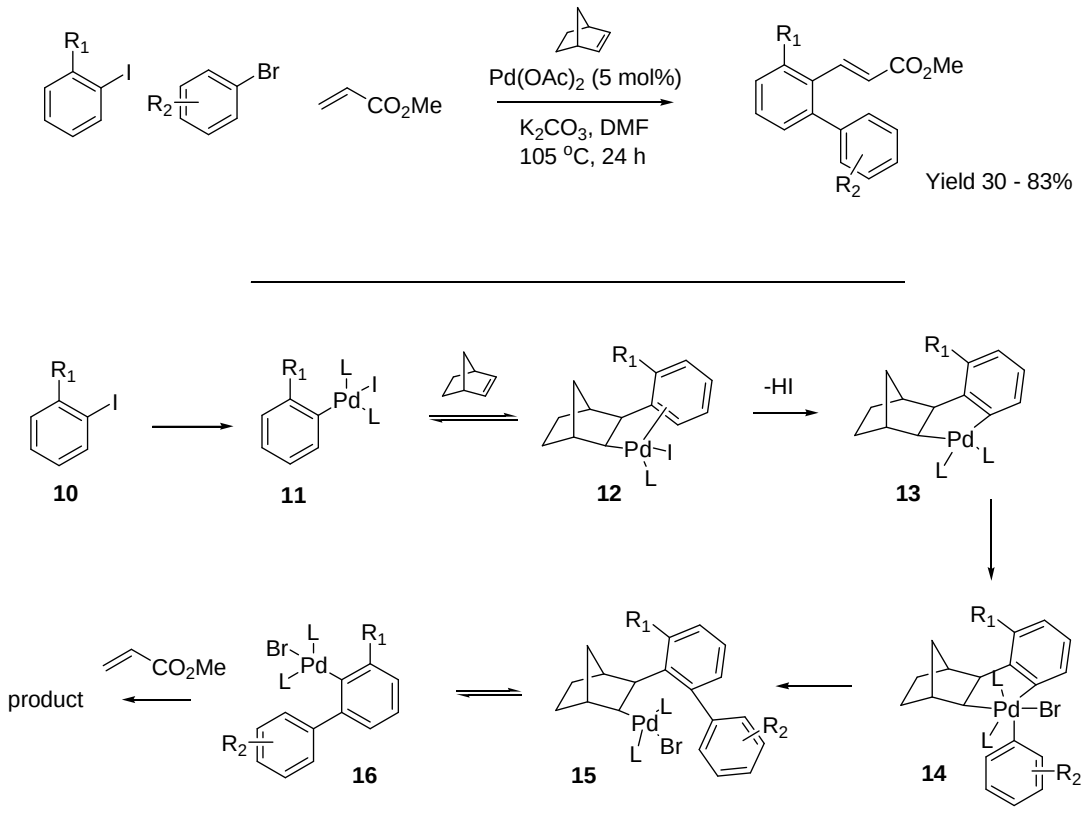


Figure 1.12 C-H activation as part of a multi-component reaction sequence

Although norbornene is technically acting as a catalyst in the reaction, a stoichiometric quantity is required, otherwise competing reaction of the acyclic alkene would produce unwanted by-products. Perhaps most impressive is that no reactant is required to be in a large excess, equimolar quantities of aryl iodide and bromide being used along with 1.6 equivalents of methyl acrylate. The authors have also extended the work to include *o*-amide and *o*-phenol substituents on the aryl bromide which can be used to form tricyclic species; the former undergoes an alternative Buchwald termination reaction upon elimination of norbornene[25] and the latter takes part in an intramolecular Michael-type reaction upon completion of the palladium catalysed reaction sequence.[26]

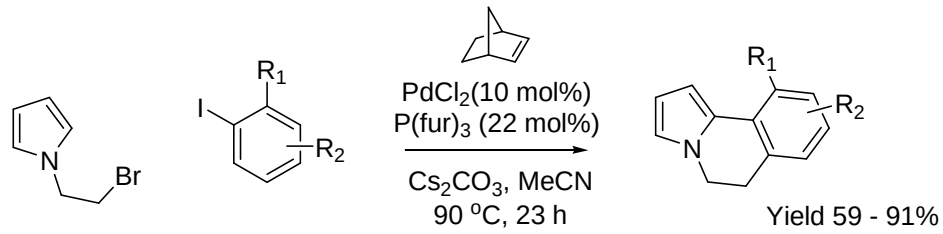


Figure 1.13 Double C-H activation through a norbornene shuttle process

Recent work from Lautens expanding on this idea has shown that 2 C-H bonds can be activated in a single process.[27, 28] Using an alkyl halide containing a suitable heteroaromatic the Heck process used by Catellani to terminate the reactions can be replaced with a C-H insertion (Figure 1.13). Again the problem of regiocontrol in the reaction is not combated, one *ortho* position of the aryl iodide being blocked in all cases, which also prevents bis-addition of the alkyl bromide. Lautens has since extended this work to the formation of tricyclic aromatics, functionalizing both *ortho*-positions of the aryl iodide by an intramolecular then intermolecular process.[29]

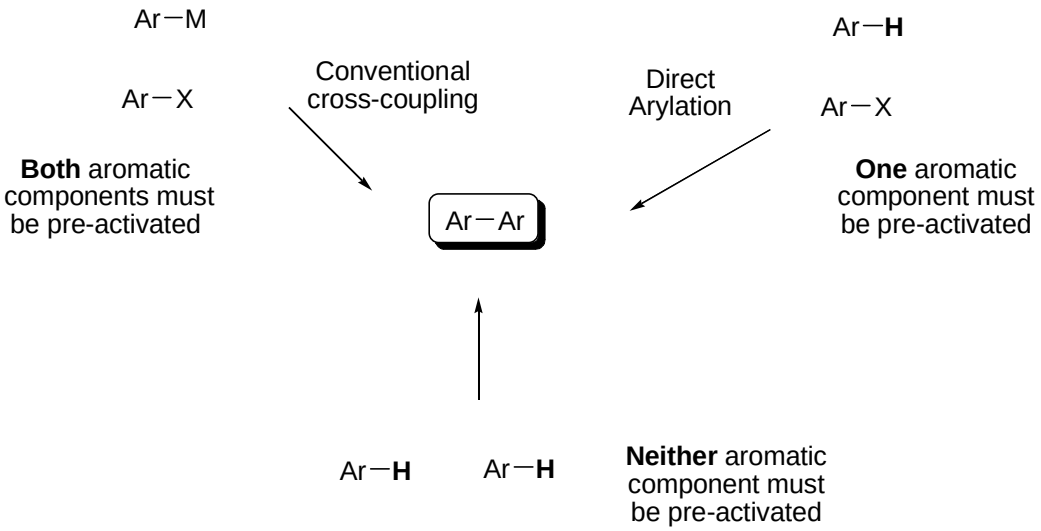


Figure 1.14 Cross coupling of unactivated aromatics [30]

Perhaps the 'holy grail' of this field would be to completely avoid substrate preactivation, by achieving the cross-coupling of two arenes through their C-H bonds (Figure 1.14). This approach is thermodynamically unfavourable due to the high bond strength of the C-H bond, in comparison to carbon-halogen bonds. Furthermore, while such an approach is alluring, the ubiquitous and diverse nature of C-H bonds present in complex organic molecules makes a regioselective oxidative coupling of this type a formidable challenge. In addition to issues of reactivity and regioselectivity associated with this reaction, deleterious homo-coupling reactions that would deplete the starting materials and generate unwanted by-products must be avoided. In order to achieve this, the catalyst must be able to react with one substrate then invert its selectivity to react exclusively with the other arene (Figure 1.15). Initial studies in this area have had some limited success.

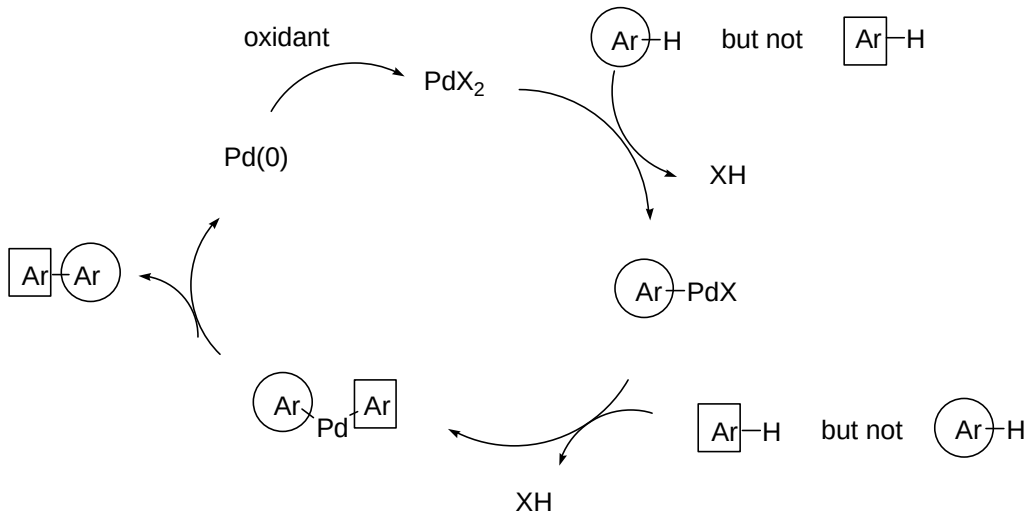


Figure 1.15 General mechanism for double C-H activation

Electron rich arenes are known to react with palladium (II) complexes via an electrophilic aromatic metallation mechanism (S_EAr). Fagnou and coworkers sought a complementary reaction. A proton transfer-palladation mechanism proved suitable, relying on arene C-H acidity rather than nucleophilicity.[30] Utilising unsubstituted or symmetrical arenes in place of the aryl halide component and indoles as a replacement for the organometallic species, good yields and reasonable selectivities for this coupling have been reported (Figure 1.16). A stoichiometric amount of copper acetate was required in order to regenerate the Pd (II) species. Although preactivation of substrates was avoided, large quantities of metal waste were generated by this process. Two other additives, pivalic acid and 3-nitropyridine, were required for successful reactions and the arene is used in a significant (30 times) excess with no mention being made by the authors as to the propensity for the arene species to homocouple. Despite these drawbacks, this reaction illustrates that the coupling of unactivated arenes is an attainable goal.

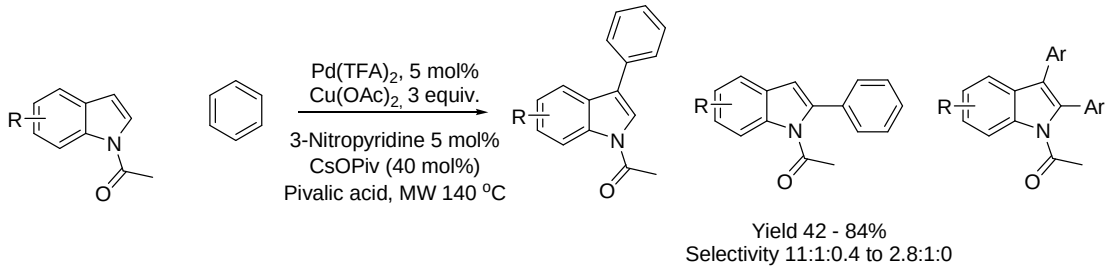


Figure 1.16 Double C-H activation forming arylated indoles

1.2 Aims and Objectives

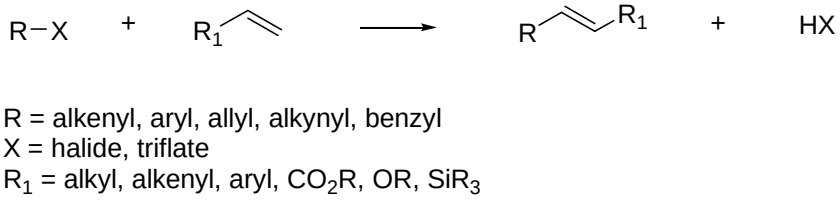


Figure 1.17 General scheme for the Heck reaction

The Heck reaction could be used as an alternative to activating the C-H bond to achieve arene cross-cross couplings without pre-activation of the substrates. The Heck reaction involves the union of an organohalide and a double bond (Figure 1.17), undergoing a similar catalytic cycle to the above cross-couplings, the product then being released by β-hydride elimination (Figure 2.2). However in contrast to the Stille and Suzuki reaction, for example, the Heck reaction cannot be used to couple an organohalide species to a phenyl derivative (Figure 1.18). This is due to the high activation energy of intermolecular carbopalladation of an aromatic carbon-carbon double bond. The advantages of the Heck reaction, allowing for palladium reactions to be carried out without a stoichiometric organometallic reagent, make this a problem worth solving.

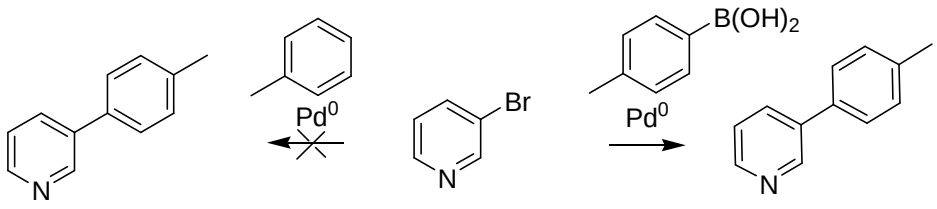


Figure 1.18 Limitations of palladium in the carbopalladation of a phenyl double bond

A potential solution to this problem would be to use benzyne as a substrate for Heck reactions. The more reactive aryne triple bond should undergo a smooth carbopalladation with an aryl palladium species. The carbopalladation product has no β-hydrogen in a suitable position for elimination and would therefore be primed to undergo a second palladium cross coupling, providing access to a myriad of 1,2-disubstituted aromatics (Figure 1.19).

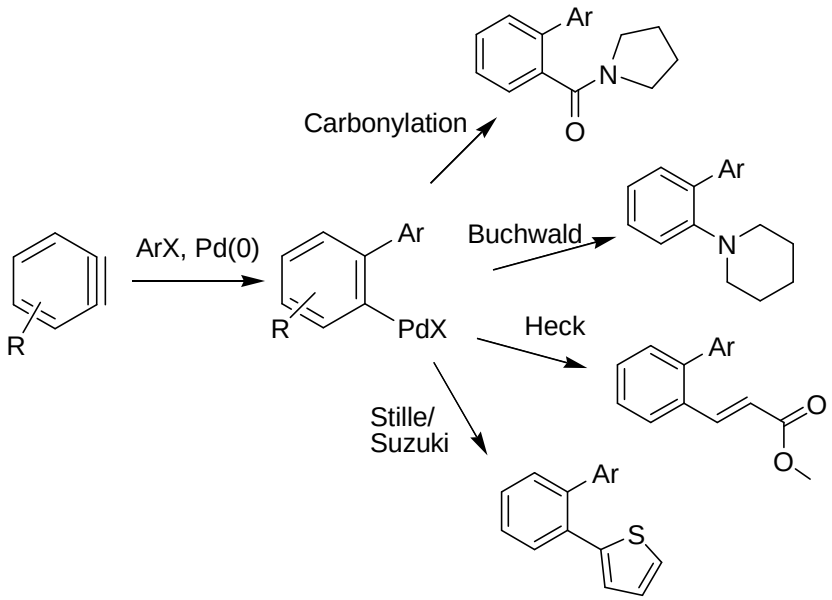


Figure 1.19 Proposed aryne carbopalladation

Along with presenting an alternative solution to the problem of arene functionalisation without the use of an organometallic reagent, the Heck reaction also allows a second transition metal catalysed transformation to take place. This provides an elegant tandem reaction and the opportunity for the synthetic chemist to design simple syntheses towards complex molecular architectures.

1.2.2 1,2-Disubstituted aromatics

The biaryl motif occupies an iconic role in chemistry, being of importance in a wide range of areas. The synthesis of 1,2-disubstituted aromatic compounds is both a complex and worthwhile exercise: there are a number of structural classes of natural products containing 1,2-substitution and, perhaps more importantly, is a motif that is often found in medicinal chemistry (Figure 1.20). Chemokine receptor antagonists, prostanoid receptor antagonists and non-steroidal anti-inflammatory drugs (NSAIDS) are just some examples of areas where 1,2-disubstitution is found as a common feature in compounds under investigation by pharmaceutical companies.

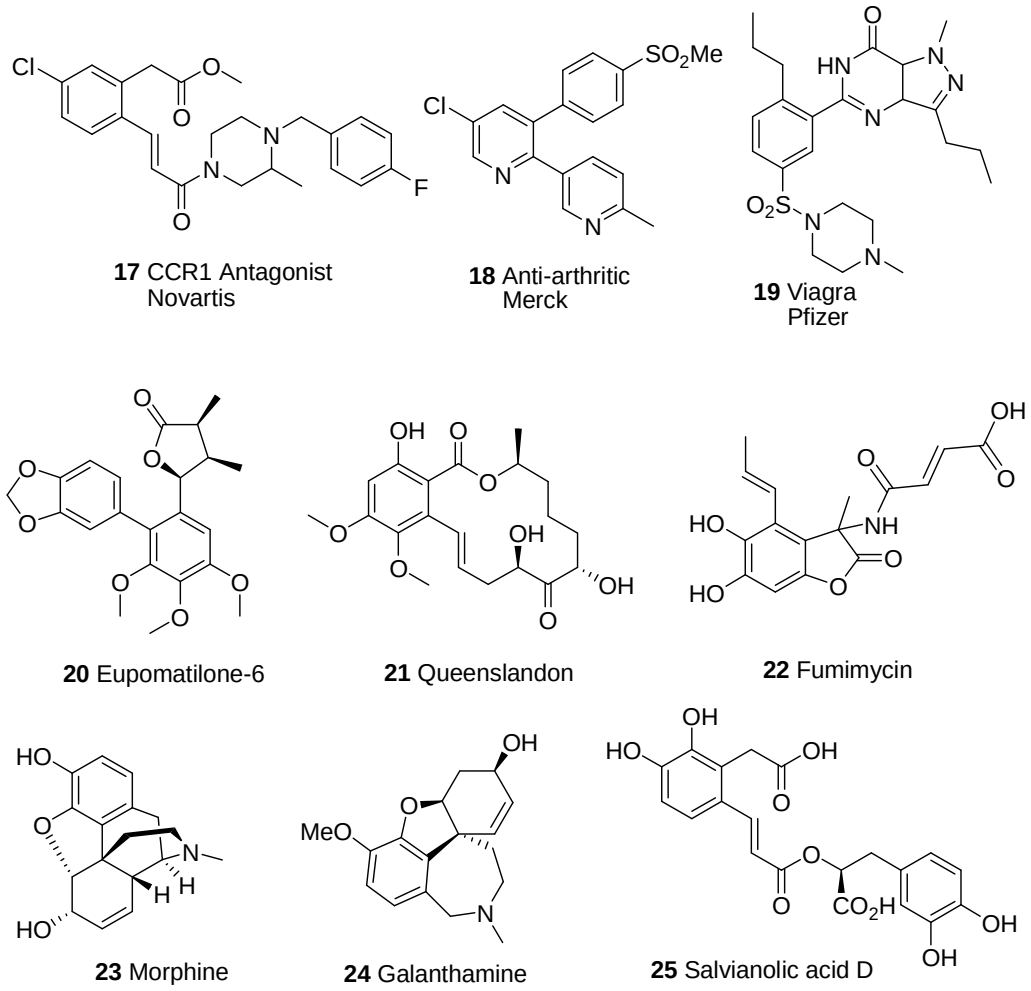


Figure 1.20 Some 1,2-disubstituted aromatic compounds

Routes to these 1,2-substituted aromatics are often lengthy. A strategy of sequential palladium catalysed cross-coupling reactions may not be suitable due to the difficulty of reacting one halide selectively in the presence of a second halide or other functional group. Where sequential cross couplings are used the second cross-coupling reaction may produce an attenuated yield or require more forceful conditions, due to steric hindrance. To combat these problems a palladium catalysed cross-coupling reaction can be used in conjunction with more classical chemistry. Alternatively, a sequence of classical functional group manipulations and C-C bond forming reactions can be employed, however these syntheses can be protracted, give low overall yields and employ hazardous or toxic reagents.

In the recent synthesis of the core of Salvianolic acid D **25** (Figure 1.20) seven steps were required to form the carbon skeleton, in an overall yield of 49%, the key steps being a Claisen rearrangement, Lemieux – Rudloff oxidation and Knoevenagal condensation.[31] In contrast, a route to this structure via a palladium catalysed benzyne coupling could yield the same intermediate in a single operation (Figure 1.21).

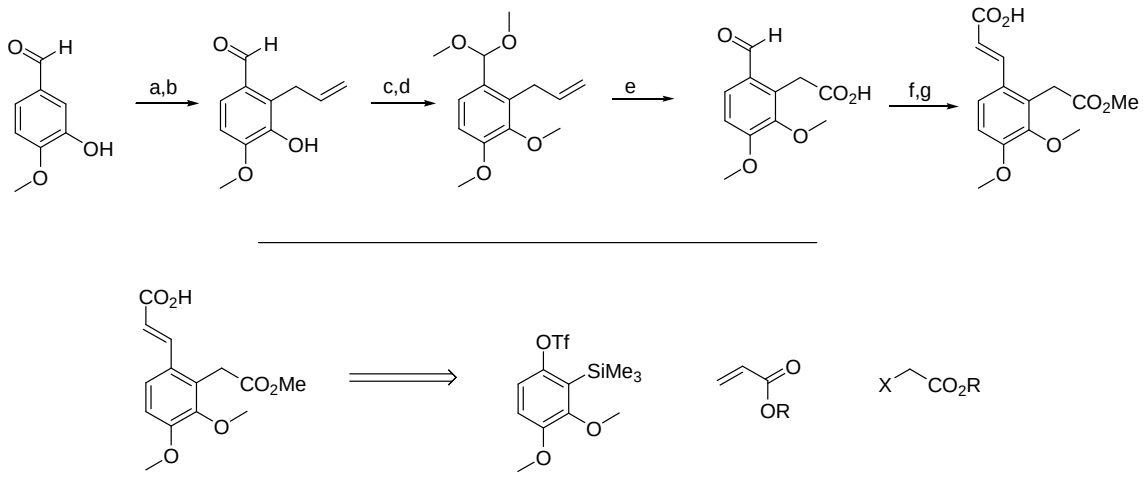


Figure 1.21 Recent synthesis of Salvianolic acid D and proposed route from benzyne. *Reagents and conditions:* a) allyl bromide, K_2CO_3, acetone, reflux, 3 h; b) DMA, reflux, 10 h; c) MeI, K_2CO_3, DMF, r.t., 10 h; d) $HC(OMe)_3$, MeOH, NH_4Cl, reflux, 2h; e) $KMnO_4$, $NaIO_4$, K_2CO_3, *t*-BuOH-H_2O, r.t., 4 h; f) $SOCl_2$, MeOH, 0 ºC, 1.5 h; g) malonic acid, pyridine, piperidine, 60 ºC, 1.5h.

1.3 Benzyne

1.3.1 100 Years of History

The existence of arynes as reactive intermediates was postulated over 100 years ago by the Germans Kahlert and Stoermer,[32] benzyne itself being proposed initially in 1927 by Clarke.[33] It took more than 50 years for definitive evidence of the symmetrical intermediate to be established, much of the work coming from the groups of Wittig, Roberts and Huisgen.[8] Perhaps the most famous of these experiments was reported by Roberts in 1953 where he showed that ^{14}C radiolabeled chlorobenzene formed a 50:50 mixture of regioisomeric radiolabeled aniline upon treatment with sodium in liquid ammonia (Figure 1.22).[34]

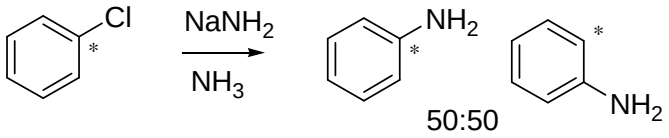


Figure 1.22 Roberts' 1953 experiment with ^{14}C radiolabelled chlorobenzene

Over the past 50 years scientists have been able to use spectroscopic methods such as UV and NMR to observe benzyne directly and this, along with theoretical calculations, have given researchers a wider insight into its nature. Benzyne is commonly represented by a triple bond (**2**) although a number of different structures, for example a diradical (**26**) or zwitterion (**27**), have been proposed (Figure 1.23). These techniques have shown that benzyne possesses some elements of these four structures, with the triple bond structure being the most accurate.[8] Though it has similar characteristics to alkynes the benzyne triple bond is highly strained and more reactive. Its most pronounced characteristic is its powerful electrophilicity caused by its low lying LUMO.

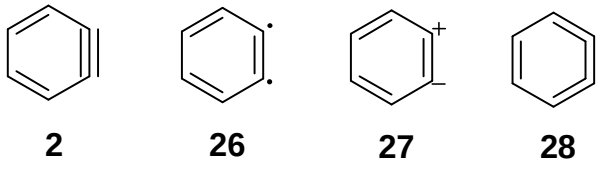


Figure 1.23 Proposed representations of benzyne

Ortho-benzyne, formally 1,2-didehydrobenzene, is just one of three possible structures that could be formed by the formal loss of hydrogen from benzene. *Meta*- and *para*-benzyne (**29** and **30**) are also known though these have been observed solely through spectroscopic techniques and theoretical studies and have not been used in synthesis, although *para*-benzyne is an intermediate in the Bergmann cyclisation (Figure 1.24).[35]

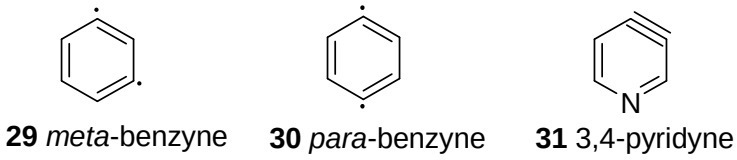


Figure 1.24 Alternative aryne structures/Heterocyclic arynes

Heterocyclic benzyne derivatives have also been reported. Although their history dates back even further than that of benzyne, Kahlert's first postulations on these species concerning a hetaryne, they are on the whole poorly characterised, with scarce physical data. Evidence for didehydrofurans, -thiophenes and –pyrroles has been gathered through trapping experiments but no direct spectroscopic measurements have been made. This may be due to the compounds tendency to undergo ring opening reactions, presumably due to increased ring strain. Of the six-membered heterocycles, pyridynes have received the most attention, with 3,4-pyridyne (**31**) being shown to display many characteristics similar to benzyne. Data on these species is still relatively scarce compared to that of benzyne itself, and there are few reports on methods of their formation or uses in synthesis.[36-39]

1.3.2 Aryne Generation

Over the past 50 years the use of benzyne in synthesis has grown, illustrated in particular by its use in a number of renowned natural product syntheses.[40, 41] As a reactive intermediate benzyne cannot be stored or handled as the isolated species and must therefore be generated *in situ*. Along with classical techniques for its production, such as that employed by Roberts, there has been significant research into novel methods of generating arynes.

Some of the earliest methods employed strong bases such as organolithiums or sodium amide to generate benzyne from halobenzenes.[42] The base removes the *ortho*-proton, generating benzyne via the anion (Figure 1.25). However, the bases used are most often nucleophilic and thus the products obtained are those from the addition of the base. For example, anilines are formed when sodium amide in liquid ammonia is used (Figure 1.22). Alternatively, a 1,2-dihalogenated aromatic can be used which generates the aryne via elimination.[6, 37, 42]

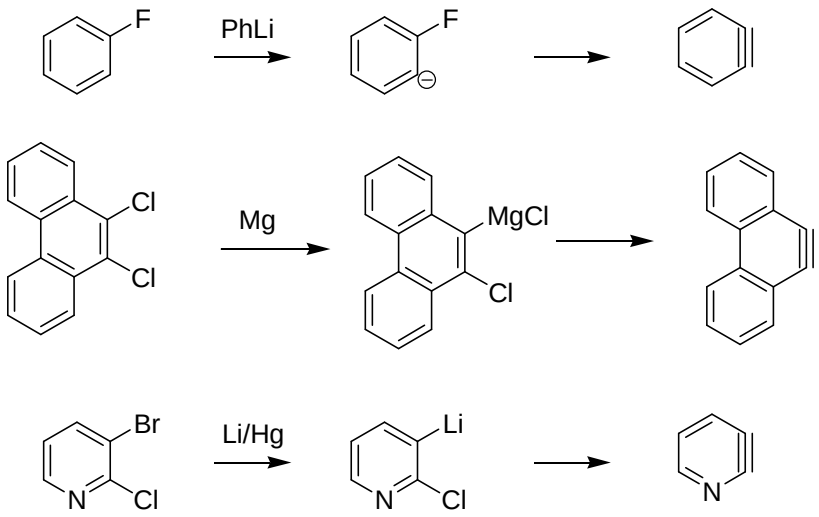


Figure 1.25 Generation of arynes from halogenated aromatics.

Similar to these methods, recent research has addressed alternatives to halide substituents for the formation of arynes. Ideal alternatives to the halides should

undergo a more facile *ortho*-metallation whilst still eliminating rapidly to allow for efficient generation. Success has been achieved with thianthrenium perchlorates **32**, triaryl selenium triflates **33** and aryl sulfonates **34** and **35**, the latter being the most broadly applicable due to their straightforward synthesis from phenol (Figure 1.26).[6, 43, 44] Use of these alternatives allow generation to be carried out at ambient temperature and are also compatible with forming halogenated arynes. However, base derived side products and competing deprotonation can decrease yields in these transformations. In particular, aryl sulfonates undergo a base promoted anionic thia-Fries rearrangement, which can consume up to 80% of the aryne precursor depending on the substituents present.[45]

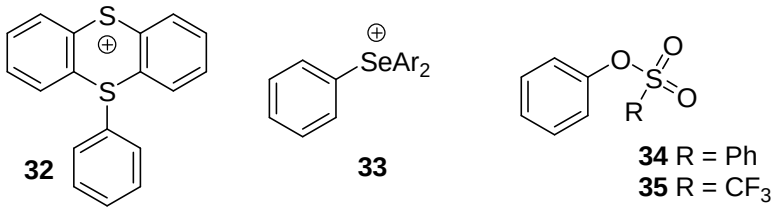


Figure 1.26 Generation of arynes *via ortho*-metallation

An important recent development in this area has come from the group of Knochel. Arynes are formed by the elimination of 2-magnesiated diaryl sulfonates **37**, which are prepared from the corresponding iodides **36** by treatment with *iso*-propylmagnesium chloride.[46] Again this chemistry involves low temperatures, the arylmagnesium precursors being generated at -78 ºC, followed by warming to room temperature allowing decomposition to the aryne. This chemistry has also been applied to the formation of 3,4-pyridynes **38**, giving excellent yields in trapping experiments with furan.[36] Where this method stands out is that aryne precursors containing a second halide are well tolerated, unlike some of the classical low temperature methods (Figure 1.27).

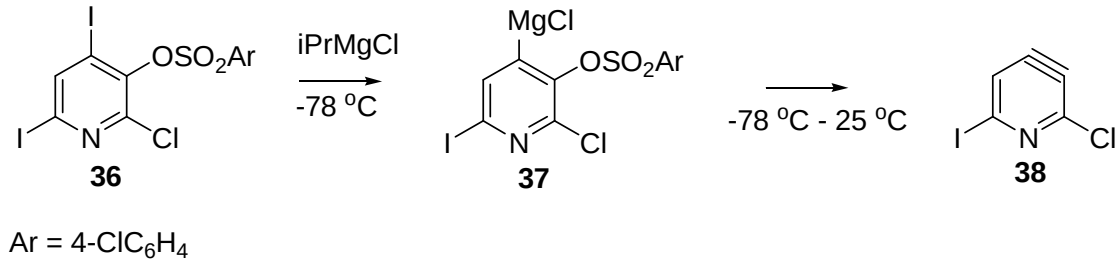


Figure 1.27 Generation of arynes from 2-magnesiated arylsulfonates

In 1963 Charles Rees reported a novel way to generate benzyne from the heteroaromatic species 1-aminobenzotriazole **39**.[47-49] Treatment with an oxidizing reagent such as lead tetraacetate or N-bromosuccinimide at low temperatures resulted in efficient benzyne generation. Two stable nitrogen molecules are formed in this fragmentation which proceeds via the nitrene; the transition state energy for the transformation being low, hence relatively mild conditions can be used. Heteroarynes such as 2,3-pyridyne **41** can also be generated from oxidation of the relevant heterocycle (Figure 1.28).[37] More recent research into this technique has been concerned with alternative heterocycles and examining different oxidising agents to assess how they affect the rate of benzyne generation, for example iodobenzene diacetate has been found to generate benzyne at a much slower rate.[50, 51]

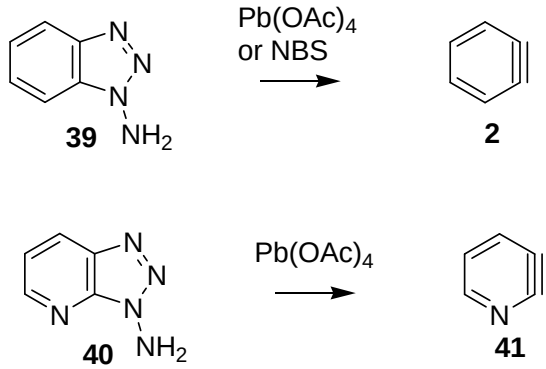


Figure 1.28 Aryne generation from heterocycles

Although many of the classical methods of generation are conducted at low temperatures; benzyne can also be generated at elevated temperatures through decomposition of zwitterionic species. The most well known example is the use of benzenediazonium-2-carboxylate **43**, which in turn is generated *in situ* from anthranillic acid **42** (Figure 1.29).[52] Decomposition takes place at temperatures under 80 °C, and can give benzyne adducts in high yields. Other zwitterionic species such as diphenyliodinium-carboxylate have been reported as being suitable for decomposition to benzyne, however rearrangement of these can occur if thermolysis conditions are not suitably harsh.[42]

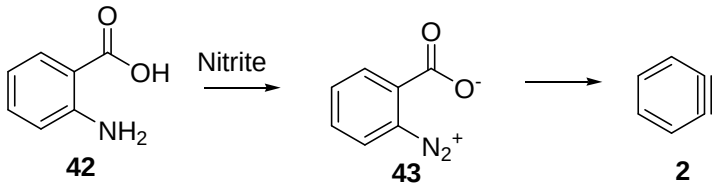


Figure 1.29 Generation of benzyne from anthranillic acid

Most of the early methods of generating benzyne employed relatively harsh conditions, be they extremes of temperature, strong bases, or strongly oxidising conditions. Evolution of benzyne is normally rapid in these reactions, as otherwise benzyne could react with its precursor, giving unwanted side-products and lowering the yields. As these conditions are not well suited to a wide range of transformations or substrates there continues to be research into alternative methods of benzyne generation.

In 1983 Kobayashi *et al* published a novel and mild method for benzyne generation *via* the fluoride induced decomposition of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate (Figure 1.30).[53, 54] Cesium, potassium or tetrabutylammonium fluorides can be used in a range of solvents at temperatures up to reflux, giving good yields in trapping experiments with furan. The idea was originally reported by Cunico who attempted to use an *ortho*-halo or tosyl group instead of the triflate. However, this approach ultimately failed to achieve satisfactory yields of benzyne, due to the rate at

which the halide is lost after desilylation, leading to protonation of the anionic intermediate. [55] Thus using triflate as a more efficient leaving group lead to an increased yield of benzyne.

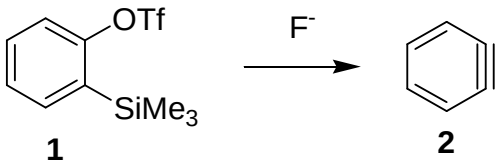


Figure 1.30 Generation of benzyne from 2-(trimethylsilylphenyl trifluoromethane sulfonate

2-(Trimethylsilyl)phenyl trifluoromethane sulfonate is a stable liquid and can be easily prepared from o-bromophenol or is commercially available (Figure 1.31). A variety of substituted aryne precursors, incorporating electron withdrawing, electron donating and bulky substituents, have been synthesized using similar procedures.[56-58] This methodology has also been extended to the generation of heteroarynes, such as 2,3- and 3,4-pyridyne.[37-39]

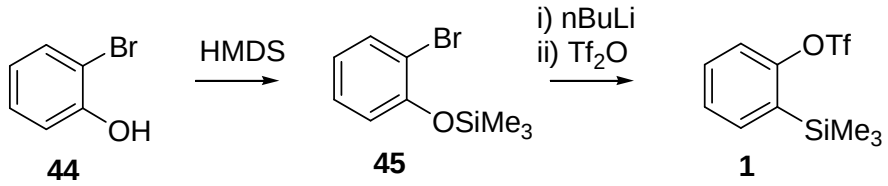


Figure 1.31 Synthesis of 2-(trimethylsilylphenyl trifluoromethane sulfonate

It took a number of years before publications using Kobayashi's method began to appear, however in the late 1990s the technique became increasingly popular, with a number of groups adopting it as their method of choice. Many of these groups are investigating the use of benzyne in metal catalysed reactions, the mild reagents and versatile conditions making this a much more appropriate method in such cases. These will be discussed later in this chapter.

Kitamura and co-workers have adapted this protocol and developed a modified reagent, (phenyl)[o-(trimethylsilyl)phenyl]iodonium triflate **47**.[59] Again the reagent can be easily prepared, from the reaction of *o*-bis(trimethylsilyl) benzene **46** and

$PhI(OAc)_2$ with triflic acid, and is a stable, crystalline solid (Figure 1.32). Benzyne is generated using TBAF or inorganic fluoride sources, giving excellent yields in a range of trapping experiments. There have been few reports of the use of this benzyne precursor in synthesis to date, and a wide range of substituted or heterocyclic variants are yet to be reported.[60]

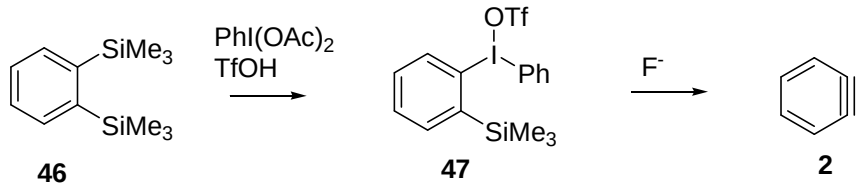


Figure 1.32 Generation of benzyne from (phenyl)[o-(trimethylsilyl)phenyl]iodonium triflate

Despite these huge advances towards the generation of arynes under mild conditions work continues on finding novel protocols. Where substituted benzynes are desired the synthetic routes to these precursors can be quite lengthy, in particular where suitable substituted 1,2-bromophenols are not available. To this end Uchiyama has developed a novel route from arylbromides using lithium dimethyl(tetramethylpiperidino)zincate.[61] The key step is deprotonative zincation, which occurs *ortho* to the substituent on the aryl bromide (Figure 1.33). A range of substituents, including amide, ester and nitrile groups are tolerated, with reactions being carried out in THF at between room temperature and reflux. There have yet to be any reported syntheses incorporating this methodology.

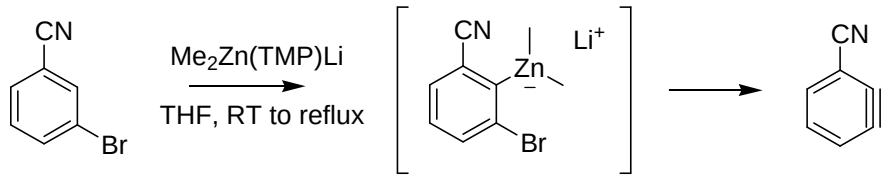
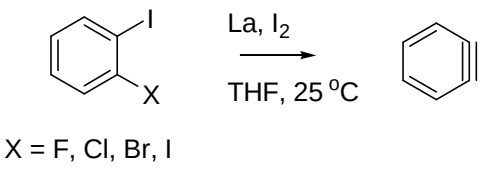


Figure 1.33 Generation of arynes using lithium zincates

A milder method of benzyne generation using *o*-dihalogenated arenes has also been recently reported. Using lanthanum metal, with catalytic iodide, arynes were generated in good yields at room temperature using THF as solvent (Figure 1.34).[62,

[63] For successful generation one of the halogens must be iodide, but F, Cl, Br and I are similarly tolerated as the elimination partner at the adjacent site.



X = F, Cl, Br, I

Figure 1.34 Benzyne generation from dihalogens at room temperature using lanthanum

1.3.3 Reactions of Arynes

Arynes are powerful electrophiles. Synthetically, they are most commonly used in pericyclic reactions and nucleophilic additions. The introduction of milder methods of benzyne generation, especially the use of silylaryl triflates as benzyne precursors, has allowed for the use of arynes in a wider range of reactions. In particular the possibility of incorporating arynes into transition metal catalysed reactions has begun to be realised. Improved conditions for both nucleophilic addition and pericyclic reactions are also being developed, with a wider range of substrate tolerance or improvement in yields being reported.[6, 7, 40]

1.3.3.1 Pericyclic Reactions

The Diels-Alder reaction is the most common pericyclic reaction in which arynes participate, reaction with furan being used as a trapping experiment to monitor benzyne generation (Figure 1.35). Due to their highly electrophilic character, arynes make excellent dienophiles and react with a wide range of dienes. The aryne Diels-Alder reaction has been applied to the synthesis of a wide range of natural products, including the gilvocarcins[64], lactonomycin[65] and Sch 47554.[66] In these examples furan is used as the diene. Little work has been reported using acyclic dienes since Wittig's initial investigations in 1964,[67] due to the competing [2+2]-cycloaddition and ene reactions that are observed. However, Lautens has recently shown that

benzyne can react efficiently with acyclic dienes, a method which was elegantly applied to the synthesis of the antidepressant sertraline (Figure 1.36).[68] Either benzenediazonium-2-carboxylate **43** or 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1** could be used to generate benzyne. The latter gave excellent diastereoselectivities when combined with dienes containing a chiral auxiliary, the former producing poor yields when combined with the chiral system.

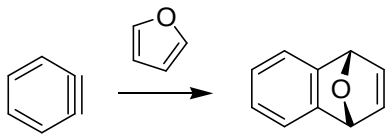


Figure 1.35 Diels-Alder reaction with furan.

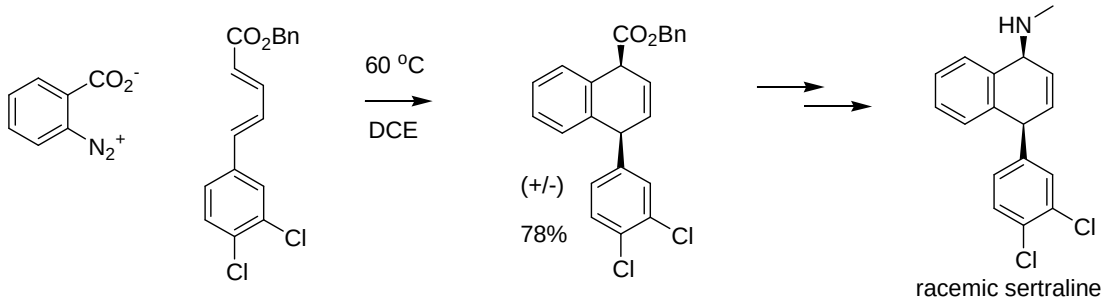


Figure 1.36 Diels-Alder reaction in the synthesis of sertraline

Although the Diels-Alder is the most common reaction of arynes, they also participate in a variety of other pericyclic reactions. 1,3-dipolar ([3+2]) cycloadditions are interesting due to the useful heterocyclic frameworks that can be formed. A recent example from Yamamoto produced indazoles from the cyclisation of arynes with diazomethane derivatives (Figure 1.37).[69] Although this and similar reactions have been previously reported using classical methods of benzyne generation, they had not been widely studied and yields were often poor.

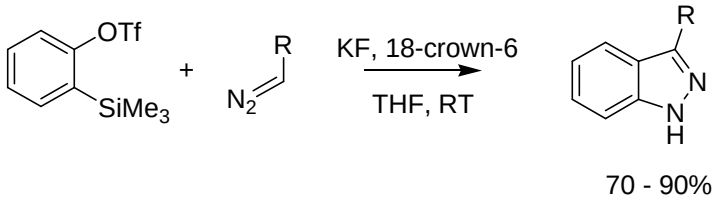


Figure 1.37 1,3-dipolar cycloadditions are useful for synthesising heterocycles

Larock recently reported the [3+2]-cycloaddition of arynes with pyridine-N-oxides, a reaction which was also previously reported to be poor yielding.[70, 71] In this case the cycloaddition is followed by a rearrangement, which occurs faster than pyridine rearomatisation under these conditions (Figure 1.38).

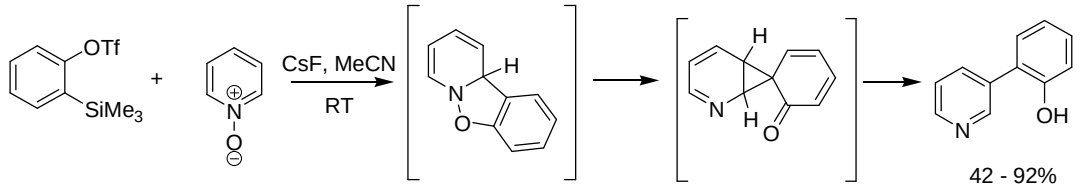


Figure 1.38 Cycloaddition with pyridine-N-oxide

The improvement gained in cycloadditions by using Kobayashi's method of generating arynes was first demonstrated in the synthesis of MK801, an NMDA ion-channel blocker.[72] 1,3-Dipolar cyclisation of the betaine, generated *in situ* from 1,2-dimethyl-4-hydroxyisoquinolium iodide proceeded efficiently at room temperature, giving an 80% yield when benzyne was generated from the silyl triflate **1** (Figure 1.39). Despite optimization of the conditions, the highest yield that could be achieved using $Pb(OAc)_4$ oxidation of 1-aminobenzotriazole **39** was 27%, whilst decomposition of the diazonium salt of anthranillic acid **43** did not give any of the desired product, highlighting the improvements that can be made through milder aryne generation.

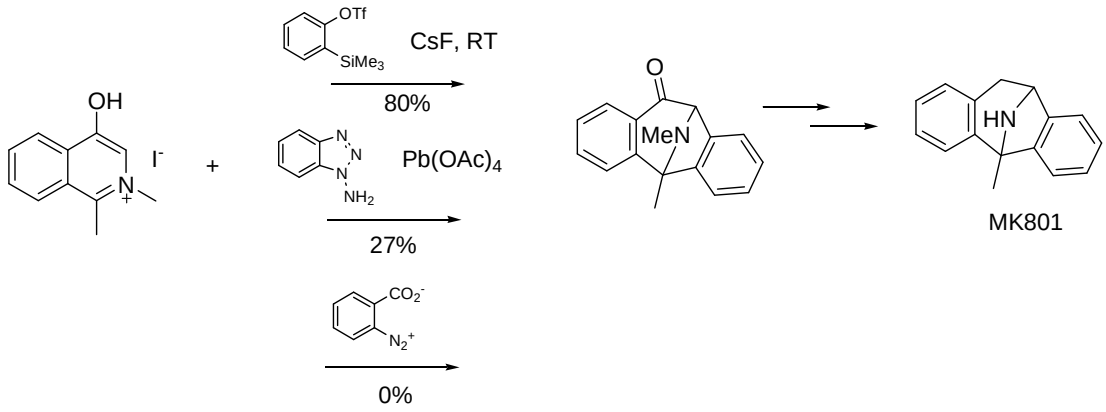


Figure 1.39 Synthesis of MK801 by 1,3-dipolar cycloaddition using different methods of benzyne generation

Arynes can also participate in ene reactions. Although an alkene is normally used in this process, the ene-products generated would presumably be more reactive towards arynes than the alkene substrates, so the authors have used alkynes in this case.[73] To avoid further reaction of the aryl allene product with benzyne an excess of alkyne was used (Figure 1.40).

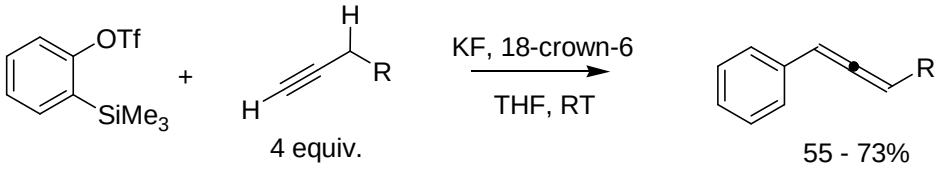


Figure 1.40 Use of arynes in the ene reaction

1.3.3.2 Nucleophilic additions

Reactions of nucleophiles with benzyne have been known for a long time, and were used to support the existence of the reactive intermediate. This is perhaps the most extensively researched area of aryne chemistry and has been used both intra- and intermolecularly in the synthesis of a number of natural products.[40] Typical examples involve the nucleophilic addition of amines or alcohols, whilst reaction with organometallic reagents containing highly polarised carbon-metal or heteroatom-metal bonds are also common. The aryl carbanion formed after the initial addition is generally trapped by an external electrophile. A recent example

from Barrett utilises the nucleophilic addition of methylallyl Grignard to an aryne in his synthesis of Clavilactone B. The aryne was generated using classical *ortho*-metallation conditions and the intermediate was trapped with an aldehyde (Figure 1.41).[74]

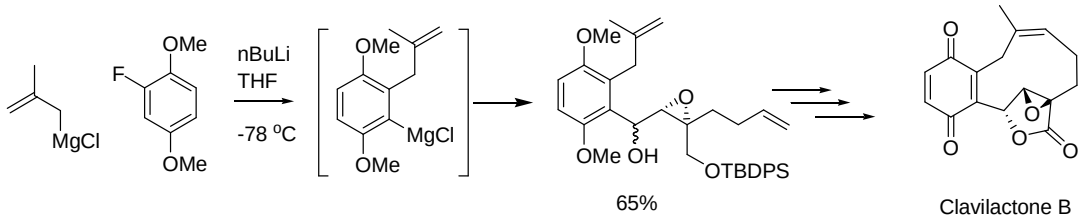


Figure 1.41 Synthesis of Clavilactone B

Due to the difficulty in generating benzyne under mild conditions, nucleophilic addition to a wide range of substrates had not been studied. Utilising the silyl triflate generation method, Larock and co-workers have published several papers detailing the wide utility of this aryne precursor for the arylation of amines, sulfonamides, phenols and carboxylic acids under mild conditions.[75-77] A wide variety of functional groups can be tolerated which would not be compatible with alternative methods of aryne generation or more conventional copper or palladium catalysed arylation reactions. Thus a two step process involving initial arylation of *ortho*-iodophenols or anilines followed by a palladium catalysed ring closure lead to excellent yields of carbazoles and dibenzofurans (Figure 1.42).[78, 79] Heteroaromatic compounds can also be efficiently arylated, reaction with imidazoles yielding N-aryl imidazolium salts which are of much interest as ionic liquids and N-heterocyclic carbene precursors.[80]

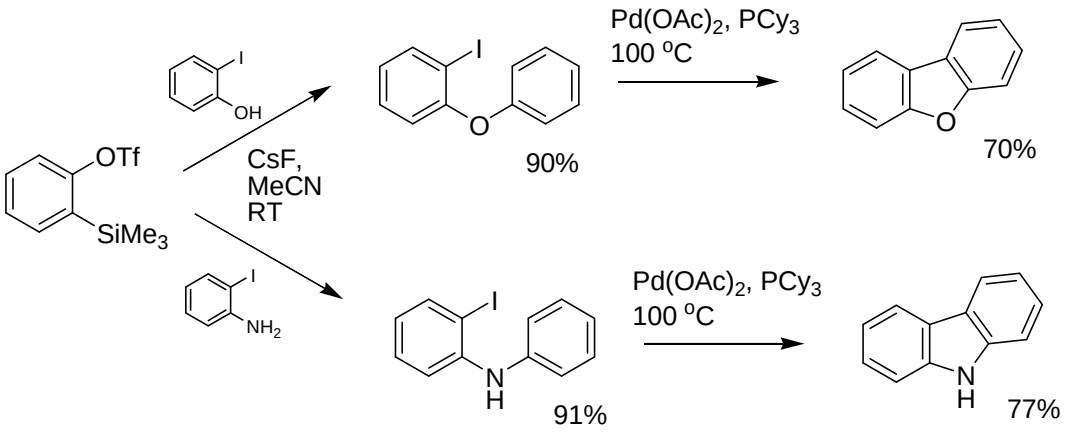


Figure 1.42 Nucleophilic addition of aniline and phenol with benzyne

Larock also demonstrated that when an electrophile is also present in the nucleophilic component it is possible to avoid protonation of the arylcarbanion and effect an intramolecular electrophilic cyclisation (Figure 1.43).[81, 82]

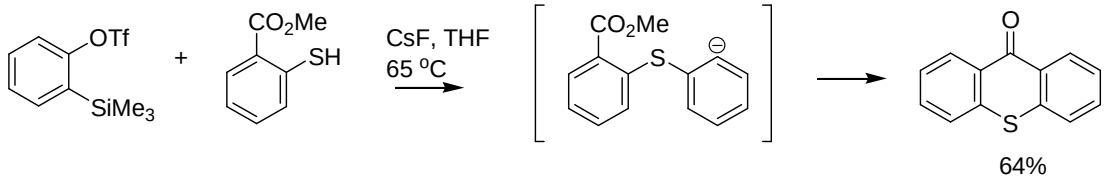


Figure 1.43 Nucleophilic addition followed by intramolecular electrophilic cyclisation

Many recent reports have concerned the addition of an element-element σ-bond across the triple bond of arynes. This method represents a powerful way to construct polysubstituted arenes. Silicon-silicon, silicon-nitrogen, tin-tin and tin-sulfur bonds are all known to undergo this insertion reaction leading to polysubstituted aromatics.[83] Perhaps more interesting is the application to carbon-carbon and carbon-heteroatom bonds bearing a suitable nucleophilic and electrophilic site. Recent work from Stoltz[84] and Yoshida[85] demonstrated that arynes can be inserted into the α,β-carbon-carbon bond of β-ketoesters and 1,3-diketones. CsF is a suitably strong base to deprotonate these species, the anion formed nucleophilically reacting with benzyne to generate the four-membered ring, in a 2+2 addition, which then rearranges to generate the observed products. This reaction is applicable to both cyclic and acyclic precursors and has since been applied to the efficient construction

of the carbon skeleton of amurensine (Figure 1.44).[86] Similar insertions into amides, sulfinamides,[87] α-cyanocarbonyls,[88, 89] α-cyanophosphonates[90] and acid chlorides[91] have also been reported (Figure 1.45).

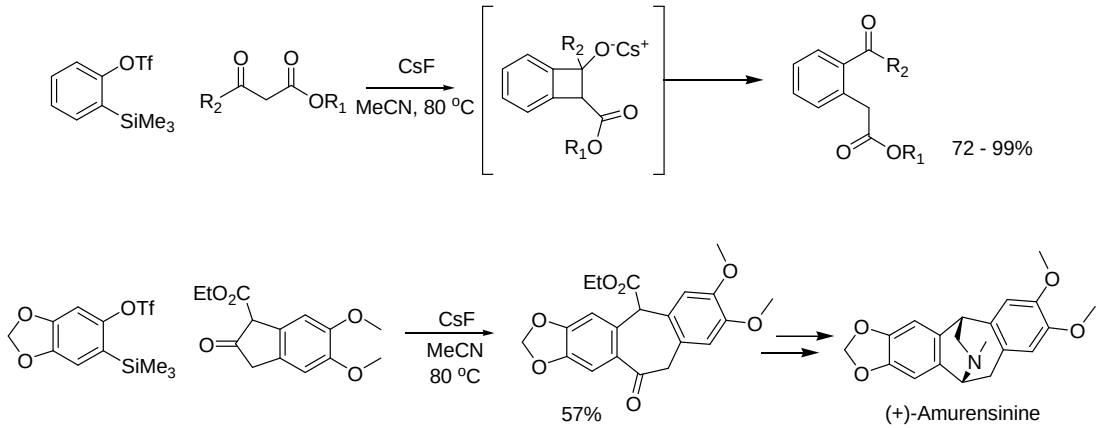


Figure 1.44 Insertion of benzyne into carbon-carbon σ-bond

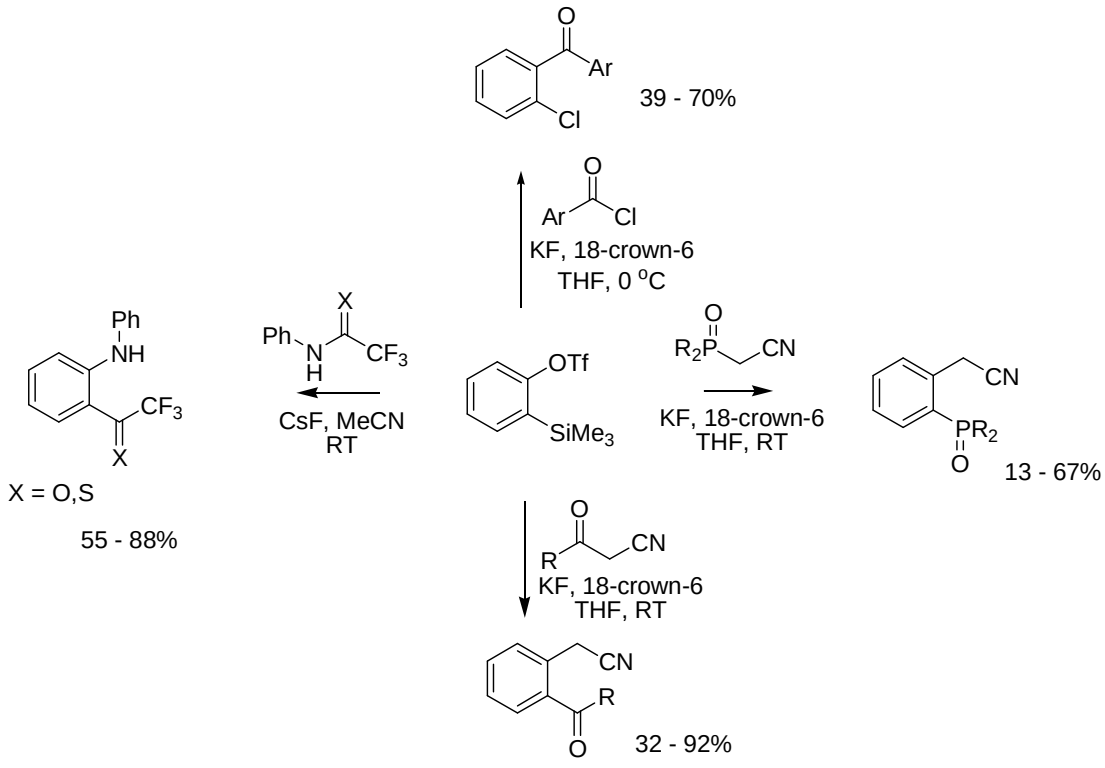


Figure 1.45 Insertion of arynes into carbon-carbon and carbon-heteroatom bonds

Nucleophilic additions of arynes are also being combined into tandem processes. When a suitable electrophilic site is not present on the nucleophile, the carbanion

generated can be trapped with an external electrophile in a three-component coupling process. This has been elegantly demonstrated recently by Yoshida, who synthesised benzoxazinones through nucleophilic attack on benzyne by an imine followed by interception of the carbanion by carbon dioxide (Figure 1.46).[92]

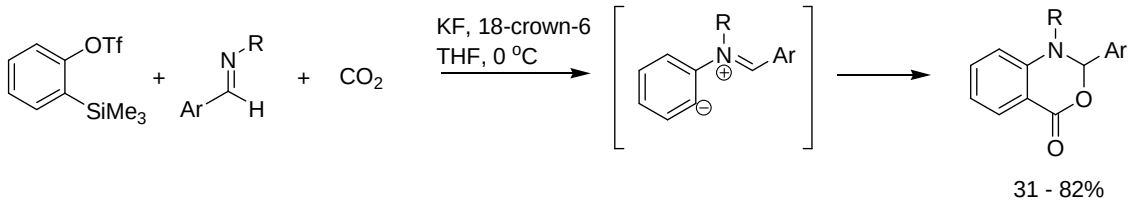


Figure 1.46 Nucleophilic addition to benzyne followed by interception of the carbanion by an external electrophile

In a similar manner Yoshida has shown that even in the presence of an internal electrophilic site on the nucleophile, careful manipulation of the reaction conditions can allow reaction with an external electrophile, again giving a three-component reaction (Figure 1.47). Nucleophilic attack by a silyl amine is followed by addition of an aldehyde as the electrophilic component. A catalytic quantity of benzoic acid is essential for a successful reaction; the authors have shown that this initially breaks the nitrogen-silicon bond, however it must also play a role in preventing reaction of the carbanion with the N-H bond.[93]

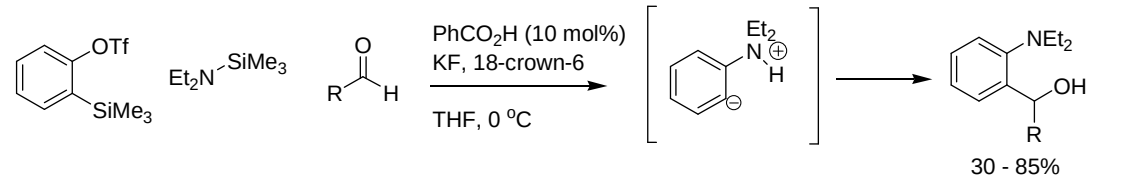


Figure 1.47 Nucleophilic addition of an aminosilane to benzyne followed by trapping of the carbanion with an aldehyde

1.3.3.3 Transition metal catalysed reactions

Until the late 1990s arynes were rarely used as substrates in transition metal catalysed reactions, in contrast to the frequent use of alkynes in these processes. Some stoichiometric reactions of zirconium-benzyne and nickel-benzyne complexes

had been studied, primarily involving the insertion of multiple bonds such as alkenes, alkynes, and CO, into the metal-aryne bond, similar to the chemistry of alkyne complexes.[94-96] However, the use of stoichiometric metal and the lack of mild and general methods for generation of the complexes mean these procedures are of limited synthetic utility. Comparing the reactivities of alkynes and arynes has led to some of the ideas behind initial forays into transition metal catalysed aryne reactions.

Early work focused on the trimerisation of benzyne and polyaromatic arynes to make triphenylenes, which are interesting due to their potential application in discotic liquid crystals and also as components of pharmacologically active compounds.[97, 98] This reaction has some precedent, however, as the trimerisation of benzyne in the presence of metals was reported as early as 1964.[99] When benzyne is generated from an organometallic system such as the decomposition of 2-fluorophenylmagnesium bromide, triphenylene **48** was obtained in an 85% yield. Guitian *et. al*. showed that arynes, generated by fluoride induced decomposition of silyl triflates **1**, trimerise efficiently in the presence of 10% Pd(0) species such as $Pd(PPh_3)_4$, with even highly strained polycycles **50** being produced in high yields (Figure 1.48).[100-102] It was noted by the authors that no triphenylene is formed in the absence of either palladium catalyst or fluoride source, evidence that the reaction involves benzyne as the intermediate and that palladium promotes the reaction.

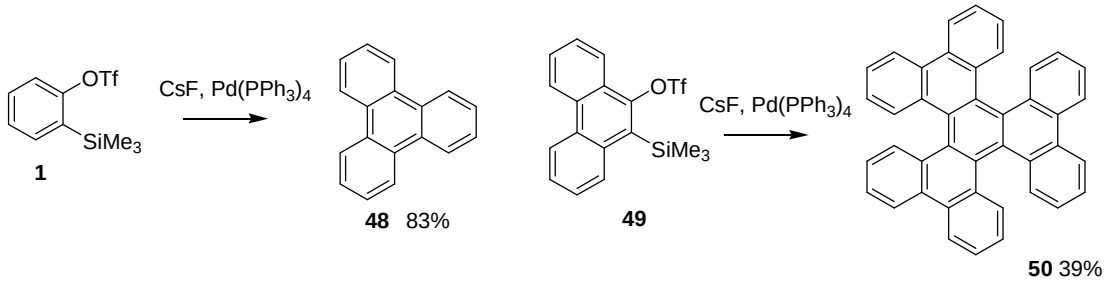


Figure 1.48 Palladium catalysed trimerisation of arynes

Formation of triphenylene can be viewed as a palladium catalysed [2+2+2] cyclisation, therefore a natural extension would be the synthesis of polyaromatic compounds via co-cyclisation of arynes with alkynes or alkenes, an area which has

received a considerable amount of interest. Initial reports concerned co-trimerisation with simple alkynes, yielding phenanthrene **51** or naphthalene **52** derivatives dependant on whether aryne or alkyne was used in excess (Figure 1.49).[57, 103-106] Bicyclic and electron deficient alkenes have also been used.[107, 108] In order to achieve regioselectivity for the cyclisation, a diyne can be used with either palladium[109-111] or nickel catalysis,[112] giving a high degree of molecular complexity in a single step as demonstrated in the synthesis of Taiwanin C (Figure 1.50).

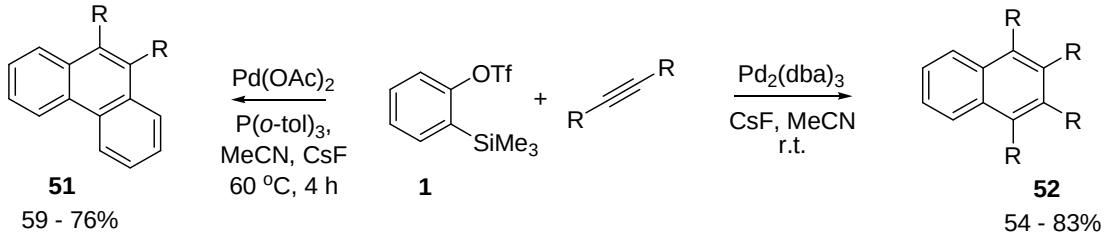


Figure 1.49 [2+2+2] co-trimerisation of arynes with alkynes

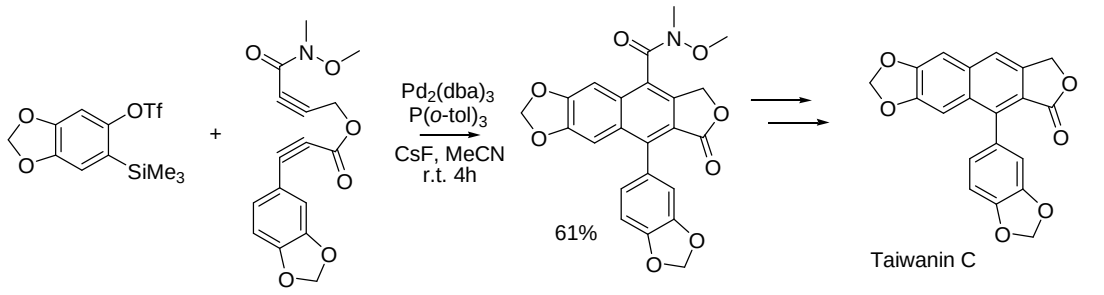


Figure 1.50 [2+2+2] co-trimerisation of a diyne with an aryne, used in the synthesis of Taiwanin C

The use of arynes as a partner in catalytic carbopalladation reactions was first reported in pioneering work by Yamamoto. This work was largely unprecedented as the intermolecular reaction of π-allyl palladium complexes with alkynes was unknown, although aryl- and vinyl- palladium complexes readily undergo carbopalladation with alkynes. They initially found that benzyne is a very reactive carbopalladation partner of π-allyl palladium complexes, producing phenanthrenes in good yields (Figure 1.51).[58, 106] Mechanistically they proposed carbopalladation of π-allyl palladium chloride **53**, formed from Pd(0) and allyl chloride, with benzyne forming an aryl-palladium species **54**. A second benzyne insertion and subsequent carbopalladation to the alkene would produce the tricyclic intermediate **56**, which

then undergoes β-hydride elimination and isomerisation to 9-methylphenanthrene (Figure 1.52).

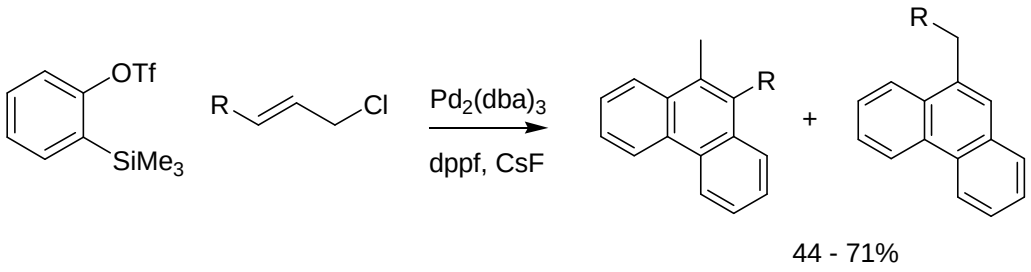


Figure 1.51 Benzyne carbopalladation of π-allyl palladium chloride, yielding substituted phenanthrenes

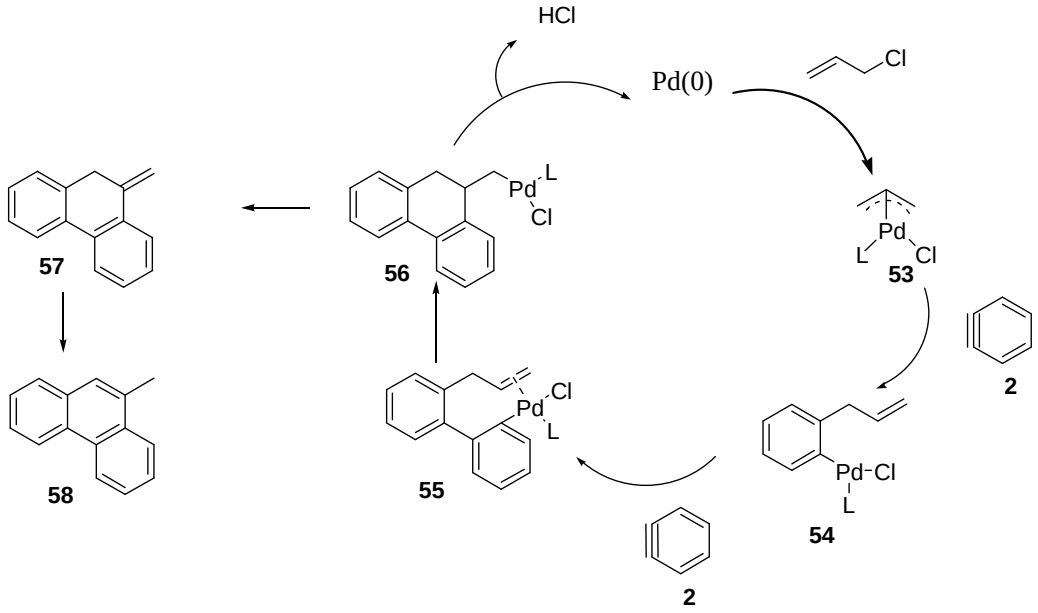


Figure 1.52 Proposed mechanism of phenanthrene formation

Yamamoto extended this method to a controlled benzyne-alkene-alkyne insertion sequence. The slow reaction of alkynes towards π-allyl palladium species makes selective carbopalladation with benzyne possible, the aryl-palladium species that is formed being active towards alkyne insertion, forming naphthalenes (Figure 1.53).

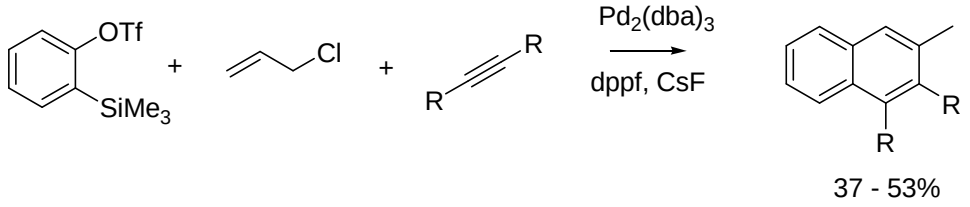


Figure 1.53 Selective benzyne carbopalladation of π-allyl palladium chloride with substituted alkynes, yielding naphthalenes.

Following on from this work, Yamamoto continued to examine the reactions of benzyne with π-allyl palladium complexes, extending the chemistry to a three-component Stille reaction. By reacting benzyne with allyl chloride and allyltributylstannane, di-allylated derivatives could be formed in high yields (Figure 1.54).[113] However it was found that if the allylic moieties of the chloride and stannane derivatives differed, completely random allylic-allylic addition was obtained. The proposed mechanism for this transformation is initial insertion of Pd into the allyl chloride followed by conversion to a bis-π-allyl palladium species via transmetallation with the stannane. Stepwise addition of benzyne to the two allyl groups would then generate the diallylated products.

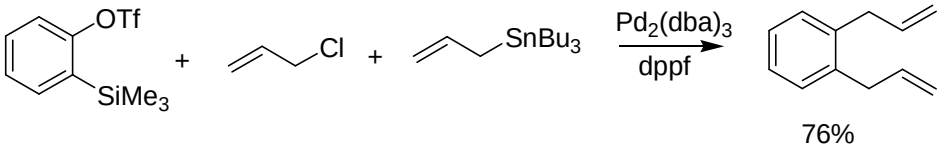


Figure 1.54 Three component Stille reaction using allyltributylstannanes

Expanding on this work, Cheng *et. al.* found that the chemoselectivity problem could be avoided by using alternative stannanes, and in particular alkynylstannanes.[114] In this case carbopalladation of the π-allyl palladium species is proposed to occur prior to transmetallation, affording high yields of 1-allyl-2-alkynylbenzenes (Figure 1.55). No phenanthrene or triphenylene formation is noted by the authors, and they do not observe any problems with selectivity. Other methods of benzyne generation, such as treatment of 1,2-dibromobenzene with lithium or decomposition of the diazonium

salt of anthranillic acid **43**, were found to be incompatible with the reaction. The authors have also extended this reaction to allenylstannanes and other organometallics, in particular the use of boronic acids in the Suzuki reaction (Figure 1.56).[115, 116]

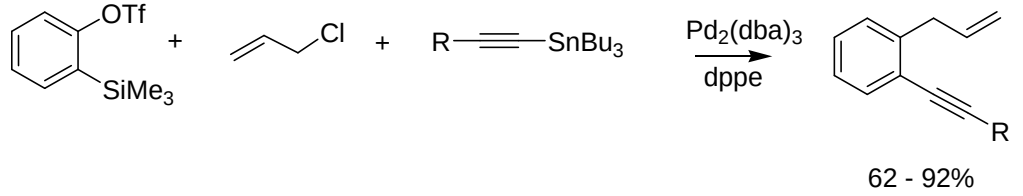


Figure 1.55 Three component Stille reaction with alkynylstannanes

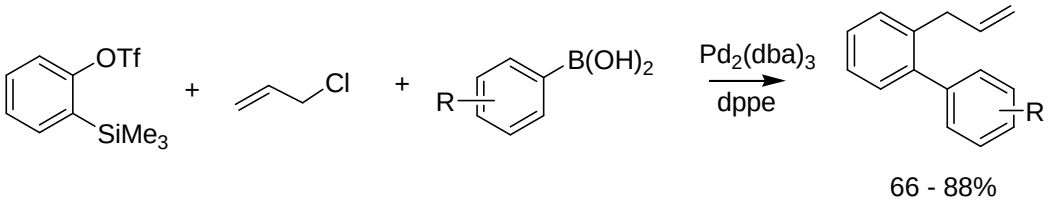


Figure 1.56 Three component Suzuki reaction with aryl boronic acids

An alternative mechanism for these three component couplings has been proposed, based on the work of Yoshida, who reported the first example of transition-metal catalysed carbometallation of arynes.[117] Reaction of alkynylstannanes with benzyne in the presence of an unusual iminophosphine ligand in combination with $Pd_2Cl_2(\eta^3\text{-}C_3H_5)_2$ as the catalyst system, produced yields of 30-54% of 1-alkynyl-2-stannylbenzenes (Figure 1.57). These could be isolated and subsequently reacted with, for example, an aryl iodide to give a 1,2-substituted aromatics. Some theoretical mechanistic studies have been carried out on this reaction using a density functional method.[118] Oxidative addition of the Sn-C σ-bond is believed to be less favourable than formation of a π-complex between aryne and palladium, the stannane then reacting with this complex. This mechanism is unusual in that a π-aryne-palladium complex has not been previously proposed as a transition state in the catalytic cycle. Although in this case the isolated yields are low, such a mechanism could be active in the previously reported three component Stille type reactions.

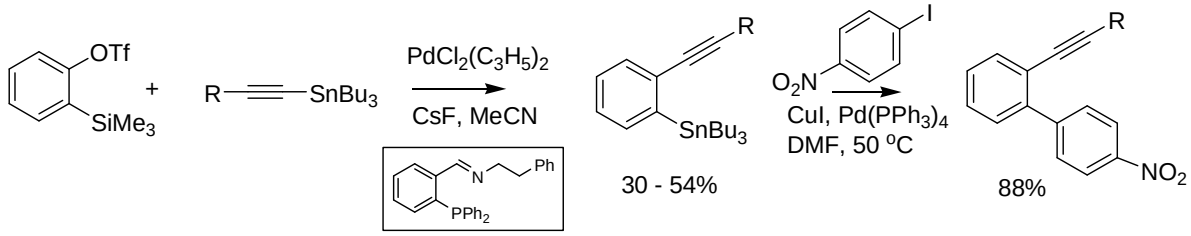


Figure 1.57 Carbometallation of arynes with alkynylstannanes

A further example of the carbopalladation of π-allyl palladium species was provided by Murai *et al*. They reported that reaction of allyl acetates with benzyne in the presence of catalytic palladium and under a carbon monoxide atmosphere yielded 2-methyleneindanones (Figure 1.58).[119] The proposed mechanism is similar to that of Yamamoto in that the aryl palladium species formed post-carbopalladation is intercepted by carbon monoxide followed by a ring closing sequence with the pendant alkene. In the same paper they also reported the first catalytic carbonylative cyclisation reactions of benzyne, furnishing anthraquinone. A number of transition metal catalysts were screened for activity in this reaction, with cobalt species giving the best selectivity and yield (Figure 1.59).

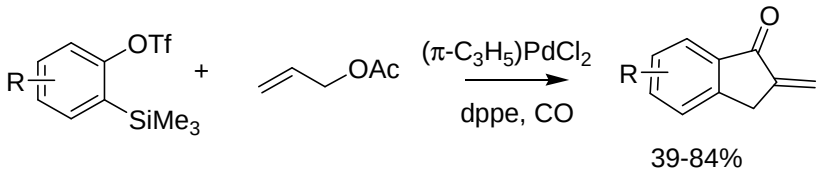


Figure 1.58 Carbonylative cycloaddition of benzyne with allyl acetate

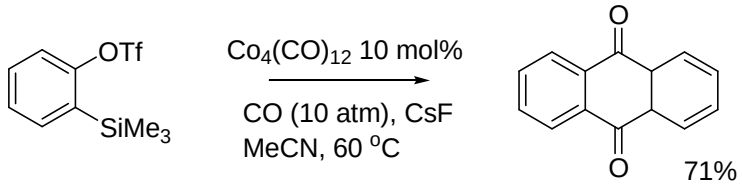


Figure 1.59 Cobalt catalysed carbonylative cyclisation

The first use of aryl halides as electrophiles in palladium catalysed aryne couplings was reported by Larock.[120] Treatment of 2-iodobenzaldehydes with arynes in the presence of a palladium catalyst generated fluoren-9-ones in good yield (Figure

1.60). A 5-fold excess of aryne precursor was required, as triphenylene by-products were presumably being formed.

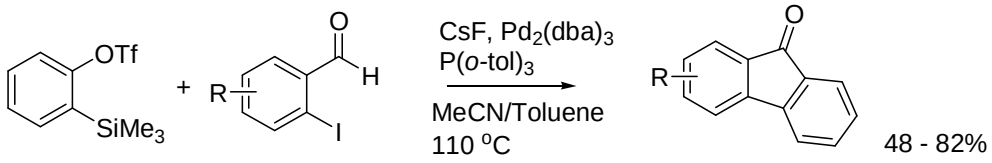


Figure 1.60 Palladium catalysed coupling of arynes with *o*-iodobenzaldehydes

Larock then went on to describe the use of biaryl halides in the formation of triphenylenes through a palladium catalysed sequence involving oxidative addition, carbopalladation of benzyne followed by C-H insertion, to form a six-membered ring.[121] The rate of benzyne generation must be carefully controlled in order to prevent trimerisation. This is achieved by varying the solvent ratio which alters the solubility of CsF. Various biaryl iodides, aryl-substituted vinyl iodides or bromides and aryl-substituted heterocyclic systems can be used, generating a wide range of polycyclic systems (Figure 1.61), a similar method also having been applied to 1-(2-bromophenyl)indoles.[122] The proposed mechanism for this reaction again involves oxidative addition of the biaryl iodide to Pd(0) followed by carbopalladation of the aryne, intramolecular C-H activation and subsequent reductive elimination. Some evidence for this mechanism was obtained by treating a stoichiometric amount of preformed aryl-palladium intermediate with benzyne. The expected product was obtained, although in a poor 22% yield, giving some support for the proposed mechanism although not ruling out other possibilities. Substituted triphenylenes can also be formed from reaction of 2 equivalents of aryne with a monocyclic aryl iodide, a reaction which has been independently reported by both Larock and Cheng (Figure 1.62).[123]

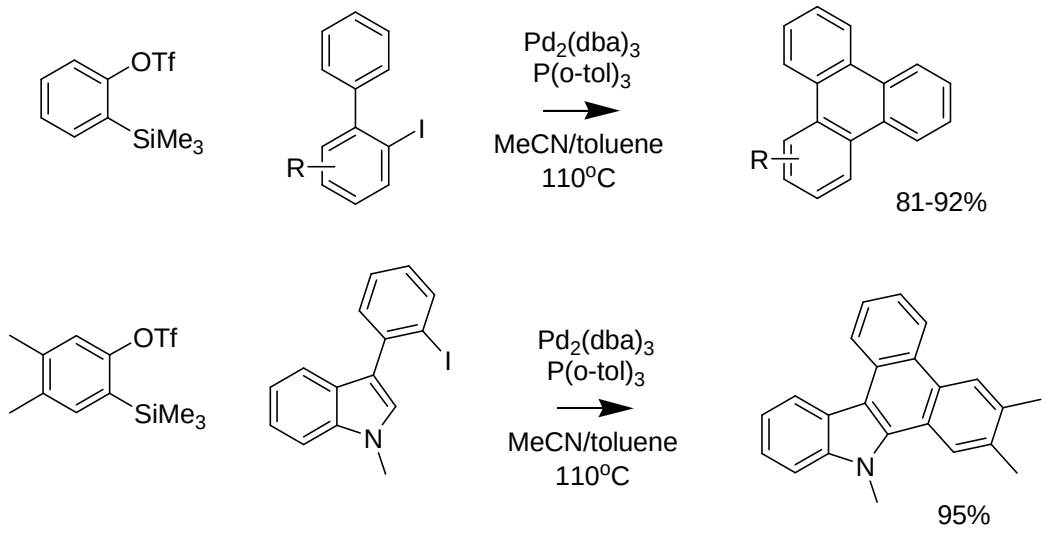


Figure 1.61 Two component coupling of a biaryl iodide and aryne forming triphenylenes.

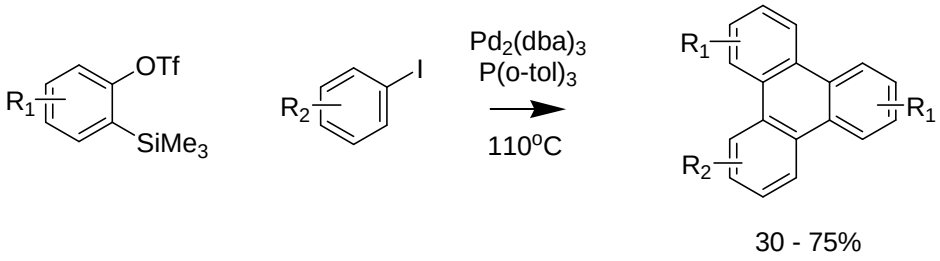


Figure 1.62 Aryl iodide – aryne – aryne coupling forms alternatively substituted triphenylenes.

This methodology has been extended by Larock to the three component coupling of an aryl iodide with an aryne and an alkyne, in a procedure that is similar to the reaction of an allyl chloride with an aryne and an alkyne reported by Yamamoto (Figure 1.51). In this case optimum reaction conditions employ a phosphine-free catalyst system along with stoichiometric $Tl(OAc)_2$, which was found to be essential to obtain successful couplings although the role it plays is unclear (Figure 1.63).[124] The authors propose a catalytic cycle that involves oxidative addition of the aryl halide to Pd(0) followed by carbopalladation of the internal alkyne in preference to the aryne, producing a vinyl palladium species **61**. Although this could theoretically undergo a second alkyne carbopalladation, this is disfavoured by the steric hindrance afforded by the bulky phenyl groups on the alkyne. Thus, carbopalladation of the less hindered aryne occurs preferentially, followed by cyclisation and reductive

elimination (Figure 1.64). Some evidence for this mechanism was obtained by subjecting a vinylic halide **67** to the reaction conditions, the product being isolated in a 95% yield. A similar reaction involving aryl iodide – bicyclic alkene – aryne coupling has also been reported.[125]

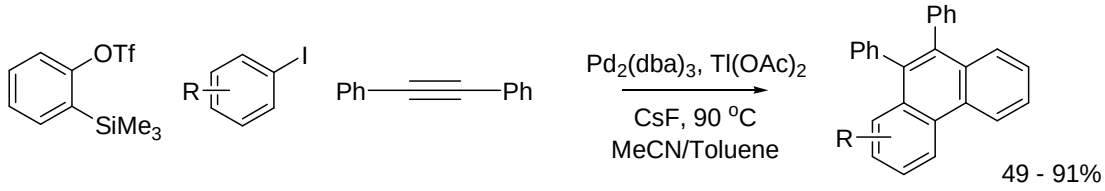


Figure 1.63 Three component coupling of an aryl iodide with an alkyne and aryne.

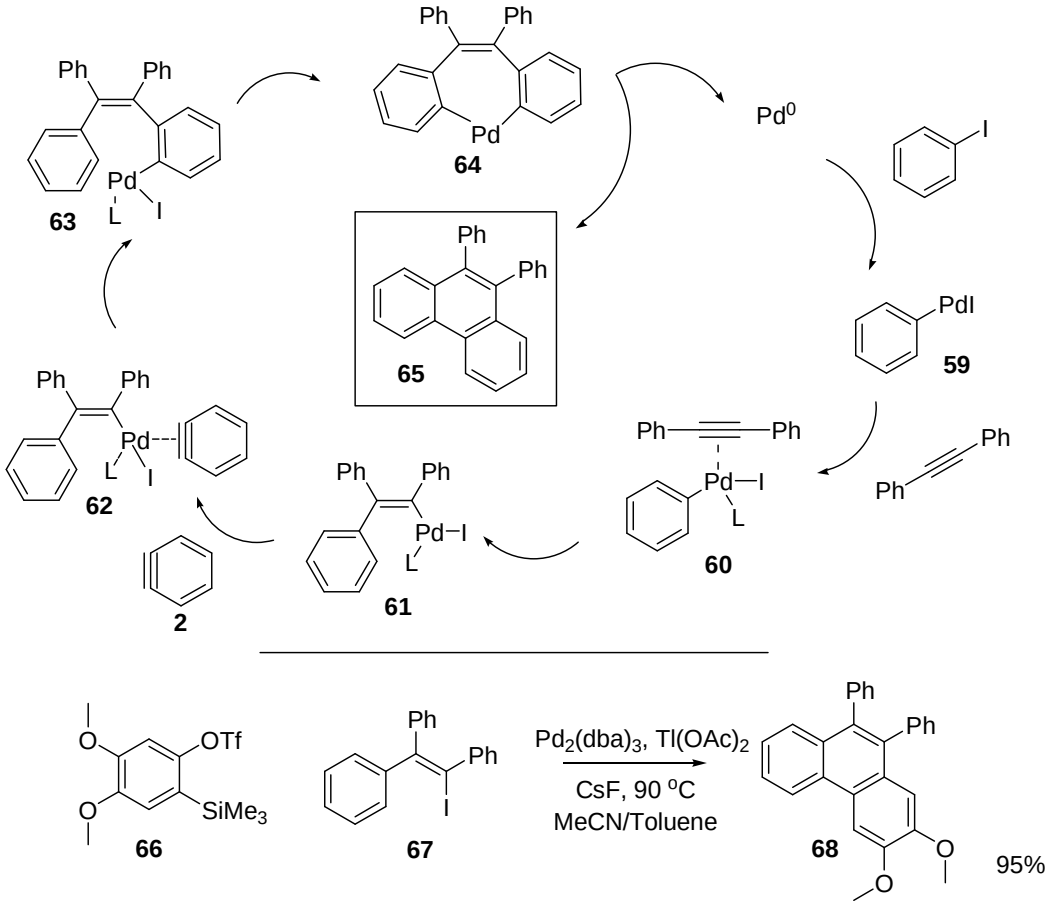


Figure 1.64 Proposed mechanism and mechanistic studies relating to aryl iodide – alkyne – aryne coupling.

Interest in other transition metals as alternatives to palladium in cross-coupling reactions has been growing. Metals such as nickel, copper or ruthenium have

advantages over palladium such as to cost, ease of handling or substrate compatibility. As nickel-benzyne complexes have previously been investigated, it is not surprising that the use of benzyne in nickel catalysed cross-couplings is also being explored. Nickel was initially employed in co-trimerisation of arynes with diynes and with alkenes,[112, 126] Cheng subsequently utilising nickel in a three component process involving alkenes, boronic acids and arynes (Figure 1.65).[127] A five-membered nickelacycle **71**, formed by the reaction of Ni(0) with aryne and alkene is proposed to be the key intermediate in this process. The authors do not comment on selectivity for the three-component coupling process *vs* [2+2+2] cycloaddition, that has previously been reported using a similar system and which is proposed to proceed via the same intermediate. It may be that the boronic acid acts as a proton source or Lewis acid which rapidly opens the nickelacycle **71**, avoiding these selectivity issues.

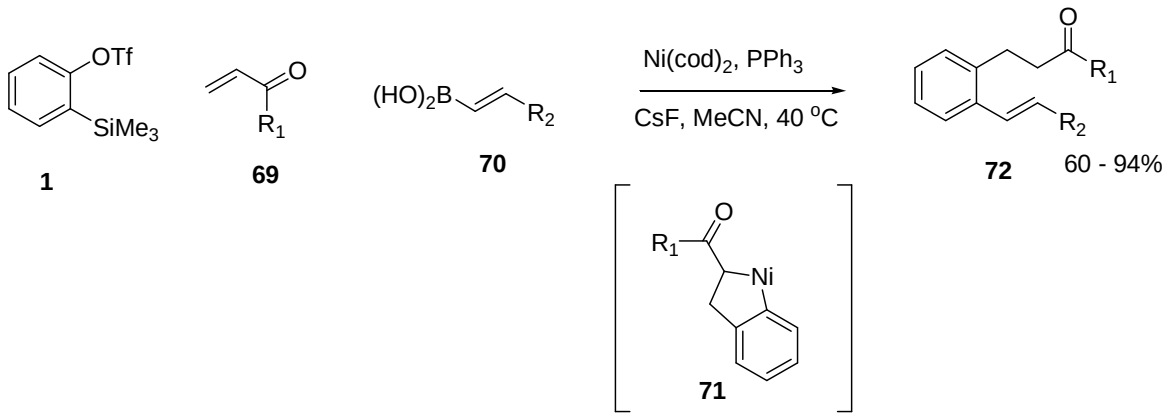


Figure 1.65 Nickel catalysed three component coupling of arynes, alkenes and boronic acids

1.4 Use of alkynes in multicomponent palladium catalysed reactions

Much precedent for the development of transition metal catalysed multi-component couplings involving arynes has come from the use of alkynes in similar processes. This field is still in its infancy, much of the pioneering work having been published during the last decade, with many of the main protagonists in the field of transition metal catalysed aryne reactions also actively pursuing research in this area.

Alkynes are primarily involved in transition metal catalysed reactions as a metallated reagent, either preformed for example as a stannane in the Stille reaction or generated *in situ* as in the Sonogashira reaction. The use of alkynes in a Heck-type reaction, where transition metals carbometallate an unfunctionalised triple bond is an area that had, until recently, received little attention. The tri- and tetra-substituted olefins that would be formed are of interest both as synthetic intermediates and as natural product and medicinal chemistry targets; Tamoxifen, which is widely used to treat breast cancer, being a well known example. Unlike polysubstituted aromatics, there are a number of classical methods for synthesising multi-functionalised alkenes, such as carbonyl olefination (McMurry, Wittig, Horner-Wadsworth-Emmons) and olefin metathesis.[128] Transition metal catalysed reactions would form a complementary route to these structures.

One of the first examples of such a reaction was reported in 1984, an aryl iodide being united with a disubstituted alkyne forming a vinylic palladium species, in an analogous reaction to the Heck (Figure 1.66).[129] Formic acid was used to cleave the vinyl palladium species to a trisubstituted alkene, through formation of the palladium hydride followed by reductive elimination. Carbopalladation did not proceed regioselectively where unsymmetrical alkynes were employed, mixtures of the two possible alkenes being obtained. Also, the authors did not determine the E/Z geometry of the alkene products, although from the mechanism it would be expected that addition of the aryl species and hydride would occur at the same side of the double bond.

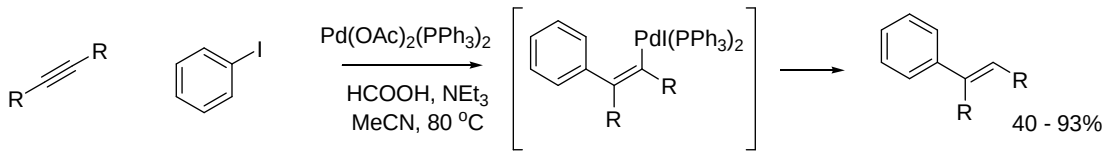


Figure 1.66 First example of alkyne carbopalladation

A similar reaction employing boronic acids instead of aryl iodides has more recently been reported, involving hydropalladation of the alkyne followed by transmetallation of the boronic acid and reductive elimination.[130] Using terminal alkynes regioselectivity for the addition of the boronic acid to the substituted end of the double bond was achieved, with internal double bonds yielding mixtures of regioisomers.

For almost a decade there was little expansion on this initial work. Many of the seminal publications in this area have come from Larock, who has since turned his attention towards aryne couplings. Initially he reported a three component coupling (3CC) involving combination of an aryl iodide, internal alkyne and a boronic acid in a Suzuki-type process (Figure 1.67).[131, 132] By utilising water as a co-solvent with DMF, excellent yields of tetrasubstituted alkene could be obtained with some selectivity. Initial addition of the aryl group from the aryl iodide generally occurs at the less hindered end of the alkyne with the boronic acid favouring the more sterically congested end, although electronic effects also play a role. The authors found the boronic acid more likely to add to the electron poor end of the alkyne, thus addition of an electron withdrawing group to the more bulky end further improves regioselectivity. For example, employing 1-(4-nitrophenyl)propyne instead of 1-phenylpropyne improved selectivity from 6:1 to 15:1. The main drawback of the reaction conditions is the requirement for both aryl iodide and boronic acid to be in three-fold excess in order to minimise the drop in yield due to the standard Suzuki reaction between these components. Similar procedures have been applied to the use of vinyl iodides in this coupling, synthesising 1,3-dienes[133] and the Pd(II) catalysed formation of tetrasubstituted olefins by addition of 2 equivalents of boronic acid to the alkyne have also been reported.[134, 135]

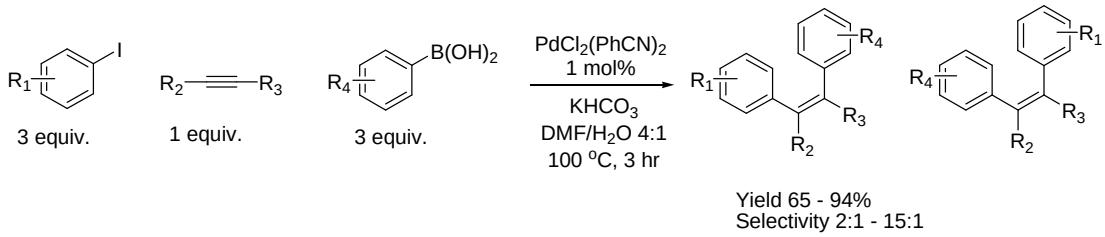


Figure 1.67 3CC of an alkyne with an aryl iodide and boronic acid in a Suzuki-type reaction

Miura has followed on from this work with the application of a similar three-component coupling to the Heck reaction (Figure 1.68).[136] Again water as a co-solvent gave improvement in yield, and the addition of lithium chloride reduced the formation of two-component Heck product. In contrast to Larock's work the alkyne was used in a four-fold excess which is perhaps reflected in their disappointing yields. Symmetrical alkynes were used in this study, thus there were no regiochemical considerations.

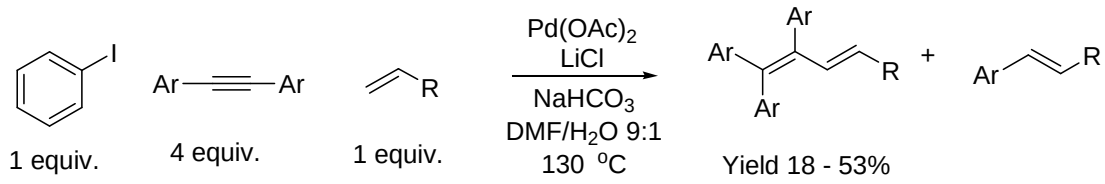


Figure 1.68 Three component Heck reaction of an internal alkyne with an aryl iodide and an alkene

As with many palladium catalysed processes, a number of groups are examining the use of alternative transition metals, leading to improvements in reaction conditions or the discovery of novel reactions. This has been particularly true in the field of alkyne chemistry with reactions catalysed by a range of metals, from gold through to iron, being reported. For example, an efficient three-component Heck-type coupling using an aryl boronic acid in place of the aryl halide has been recently reported (Figure 1.69).[137] Higher yields were achieved than in the analogous palladium catalysed process, reported by Miura, and the majority of reactions gave excellent selectivity *vs* two-component coupling. Again conducting the reaction in water is a key factor for success, the authors reported this is due to a concentration effect.

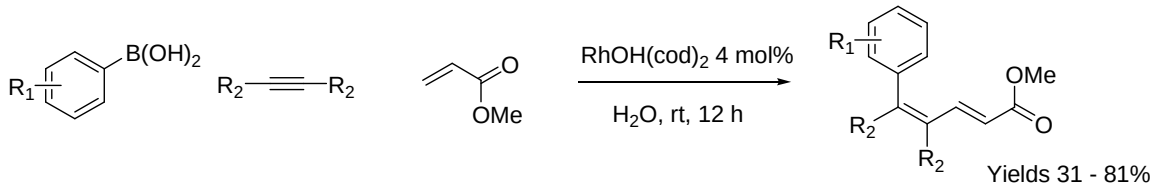


Figure 1.69 Rhodium catalysed three-component Heck type coupling

Although significant amounts of research into multi-component coupling of alkynes have been reported many hurdles are left to overcome. Yields are often low, with material being lost in the formation of two-component products or polymerisation, and regiochemical outcomes can be difficult to predict and control. These problems are sure to be repeated as related carbopalladation reactions of arynes are investigated, however with careful reaction planning and optimisation they should be surmountable.

2 The search begins – The Heck Reaction

Following the development of a mild and universal method for generating benzyne, and its initial application in palladium catalysed reactions, work was begun on the search for palladium catalysed three component couplings (3CC). At the outset of this research the Stille reaction using allyl chlorides and alkenyl stannanes was the only known 3CC not involving ring formation(Figure 1.55).[114] The Heck reaction was considered to be a suitable starting point for this research, as this would minimise the use of toxic metals and result in an interesting molecular architecture that would have potential for further manipulation. Increasing the scope of aryne 3CC reactions through incorporation of a variety of organohalides was also a priority.

2.1 Introducing the Heck Reaction

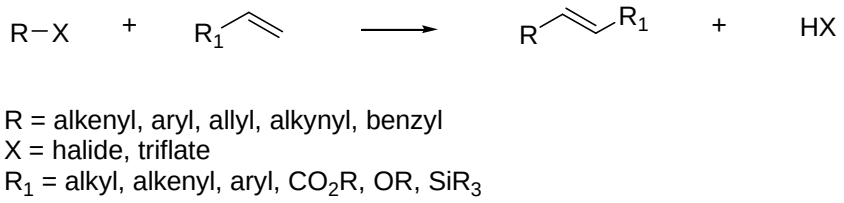


Figure 2.1 General scheme for the Heck reaction

Although commonly known as the Heck reaction (Figure 2.1), the first report of a palladium catalysed arylation of an olefin originated from the labs of Mizoroki in 1971,[138] therefore the reaction is also referred to as the Mizoroki-Heck reaction. Heck's report followed, in which the range of compatible halide electrophiles was extended.[139] The work built on Fujiwara's 1969 paper where stoichiometric palladium was employed.[140] Although now considered an important and versatile reaction for the formation of carbon-carbon bonds almost 20 years passed before the utility of this process was realised. Modern research has focused on the development of new ligand and additive systems to broaden the range of organohalides that can be

used. Sequential and cascade reactions, enantioselective variants and mechanistic investigations have also received considerable attention.[11, 141]

As shown above (Figure 2.1) the Heck reaction involves the formation of a carbon-carbon bond between an organo-halide or triflate and an alkene. A proposed mechanism for the reaction is illustrated below (Figure 2.2). Oxidative addition of the organohalide to a palladium(0) species is followed by carbopalladation of the double bond **75**. This species undergoes internal rotation **76**, after which elimination of the β-hydrogen in a syn fashion releases the product **77**. The palladium(0) species is then regenerated by elimination. This mechanism shows a neutral palladium species, however, depending on the reaction conditions a cationic palladium species has also been suggested.

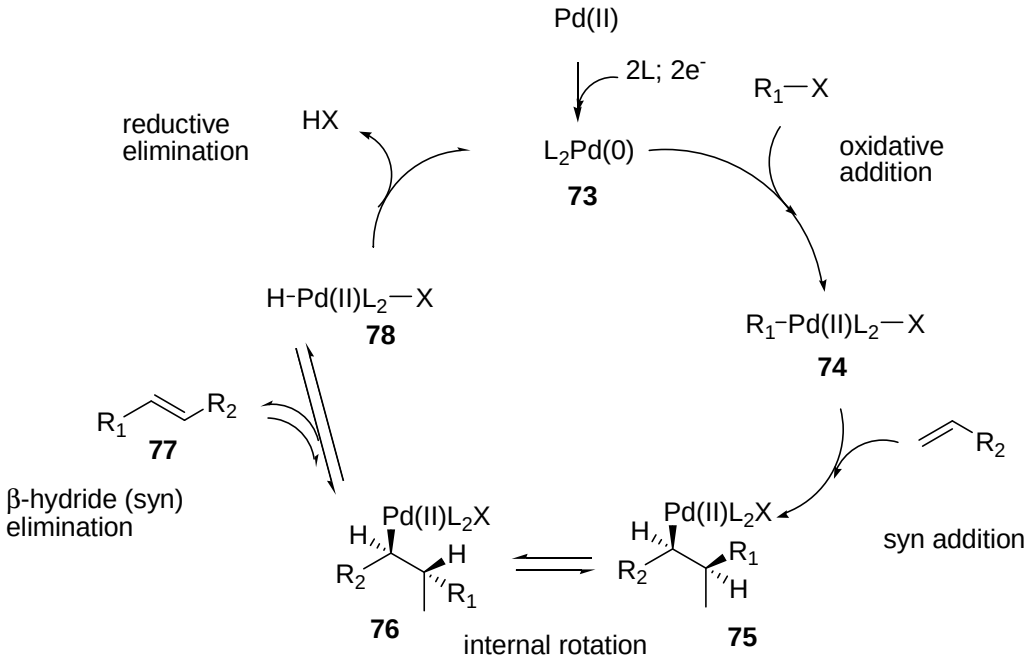


Figure 2.2 Proposed mechanism of the Heck Reaction

Originally the reaction was carried out at high temperatures, with methanol as a solvent and a palladium (II) source. A base is needed to accelerate the reductive elimination of HX from palladium, and this can be either organic or inorganic. It is now more common to use phosphine ligands along with the palladium (II) source and

this, along with other alterations to the original conditions, has broadened the scope of the reaction to include aryl bromides and chlorides along with a range of other organohalides. A variety of temperatures, solvents, bases and ligands can be employed in order to optimise the conditions for the required substrates.[11] Of these, the phase transfer conditions introduced by Jeffrey are the most widely applicable, involving the use of tetrabutyl ammonium salts in conjunction with insoluble bases, which accelerate the rate of reaction.[142] Additives, in particular silver and thallium salts, can also be added in order to improve selectivity or reaction rate.

Whilst the Heck reaction is an excellent method of forming C-C bonds it is not without its drawbacks, and these will be important to consider when choosing substrates for 3CC. Depending on the regiochemistry of syn-addition there may be more than one product formed with the new carbon-carbon bond being at either the more or less substituted end of the double bond e.g. **81** and **83** (Figure 2.3). Regiochemistry is also a problem when there is more than one β-hydrogen that could be eliminated, such as **86** and **87**. Although trans double bonds are the normal outcome of the reaction, it is also possible to yield cis/trans mixtures, normally caused by the readdition of the product to the palladium species.

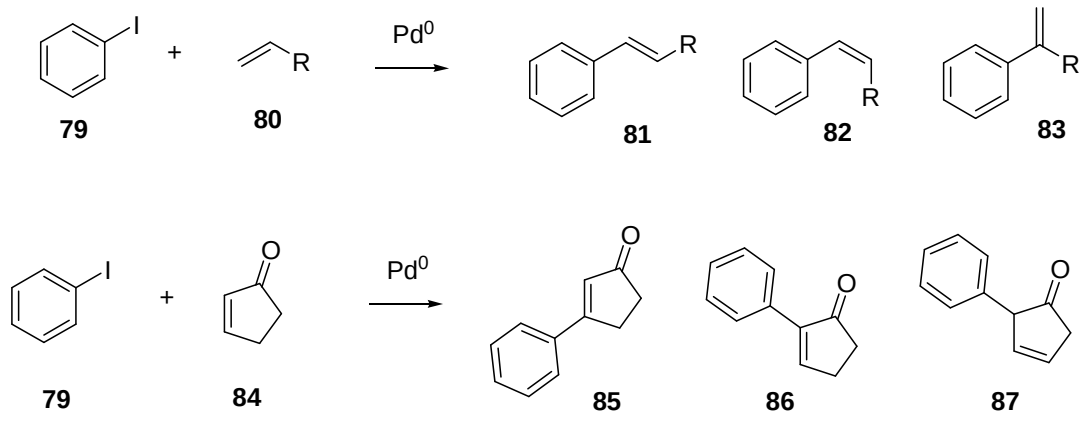


Figure 2.3 Possible regiochemical outcomes of the Heck reaction with acyclic and cyclic precursors

2.1.1 Reaction planning

The development of a three-component palladium catalysed coupling reaction involving benzyne as the central component will not be straightforward. It is however prudent to fully outline some of the potential pitfalls at the start of the project, as this may be useful when considering the myriad of reaction conditions that could be employed. To obtain useable yields it is essential that the carbopalladation of benzyne is of a comparable rate, or faster, than the reaction between the other two components. If it is considerably slower, a significant amount of undesired two component coupling product will be formed, along with the possibility of homocoupling (Figure 2.4). It is, however, also important to control the rate of benzyne generation. If this is fast and a high local concentration develops, benzyne will dimerise or trimerise, or may react with one or other of the starting materials in a co-cyclotrimerisation.

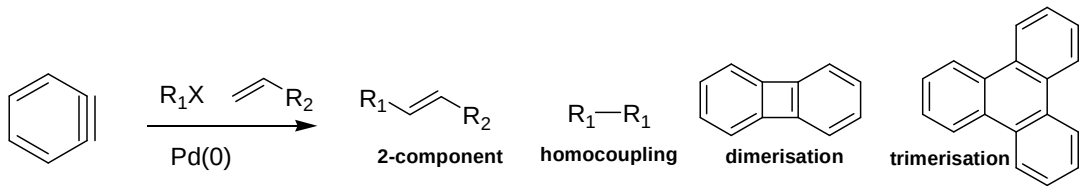


Figure 2.4 Some of the anticipated by-products

2.2 Allyl Chlorides

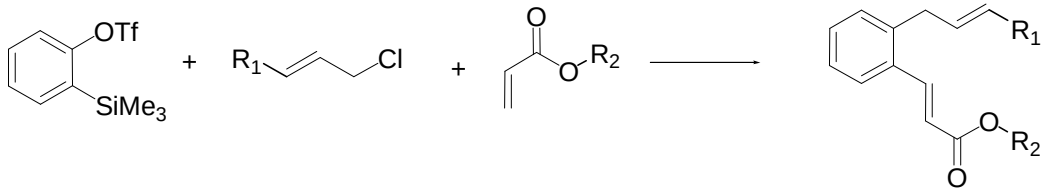


Figure 2.5 Proposed three component coupling using benzyne with allyl chloride and methyl acrylate

As silyl triflate **1** is the preferred method of benzyne generation for use in palladium catalysed reactions, and allyl chlorides have been demonstrated to be a compatible nucleophile, this left only the Heck acceptor to select. Acrylates have been reported

to give excellent selectivity in terms of regiochemistry,[143] and also give both a second handle for further manipulation along with increasing the polarity of the products which makes chromatographic separation more facile (Figure 2.5).

2.2.1 Initial Studies

The search for suitable conditions for a three component Heck reaction began with attempting to modify Cheng's Stille conditions, which were reported to give exceptional yields and few by-products (Figure 1.54).[114] In the case of allyl chlorides there is unlikely to be the predicted problem of the formation of the two-component coupling (2CC) product from direct reaction of the allyl chloride with acrylate, as this Heck reaction is not widely reported in the literature.

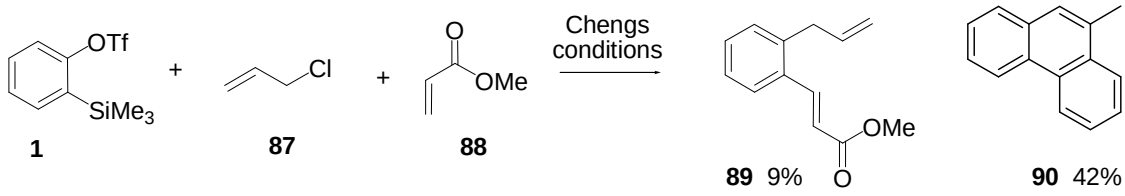


Figure 2.6 Three component Heck coupling

Initial studies into this reaction utilising Cheng's conditions showed the formation of phenanthrene **90**, from the reaction of two equivalents of benzyne and one of allyl chloride **87**, at the expense of 3CC product **89** to be a significant problem (Figure 2.6). As mentioned previously, the synthesis of benzyne-benzyne-alkene coupling product **90** was reported by Yamamoto,[58, 106] giving high yields of phenanthrene products (Figure 1.51). Cheng, however, did not report any deleterious benzyne-benzyne-alkene couplings. The conditions are contrasted below (Table 2.1).

Table 2.1 Comparison of conditions used by Cheng and Yamamoto

Parameter	Cheng (Stille)	Yamamoto (Phenanthrene)
Solvent	MeCN	MeCN/Toluene (1:1)
Catalyst	$Pd_2(dba)_3$/dppe	$Pd_2(dba)_3$/dppf
Temp	40 °C	60 °C
Time	10 hrs	24 hrs
Benzyne equiv	1.0	2.0

Utilising the same conditions as Cheng 3CC product (**89**) was isolated in only 9% yield, with 42% phenanthrene **90**. The catalyst system plays an extremely important role in benzyne reactions,[104] therefore a catalyst/ligand screen was carried out with the intention of improving the yield and selectivity for 3CC over phenanthrene formation (Table 2.2).

Table 2.2 Initial catalyst screen for Heck three component coupling

Entry	Pd source	Phosphine	3CC (89)	Phenanthrene (90)
1	$Pd_2(dba)_3$	dppe	9	42
2	$Pd(PPh_3)_4$	-	18	33
3	$Pd(OAc)_2$	PPh_3	17	24
4	$Pd(OAc)_2$	dppe	28	58
5	$Pd(OAc)_2$	dppp	mainly phenanthrene	
6	$PdCl_2(MeCN)_2$	-	0	
7[a]	$Pd(dppf)Cl_2$	-	0	
8	$Pd(PPh_3)_2Cl_2$	-	mainly phenanthrene	
9[b]	$PdCl_2$	dppe	17	
10	$Pd(OAc)_2$	-	phenanthrene and triphenylene	
11	$Pd(OAc)_2$	PCy_3	0	
12[a]	$Pd(OAc)_2$	$P(tBu_3).HBF_4$	0	
13	$Pd(OAc)_2$	dppb	mainly phenanthrene	

Reactions were carried out using a 1:1.2:1.2 ratio of **1**:**87**:**88** with 5%Pd/ligand and CsF 4 equiv in MeCN at 50 °C for 12 hrs. [a]Complex mix by HPLC/NMR but no product **89** evident. [b]54% benzyne precursor **1** recovered.

By changing the palladium source from $Pd_2(dba)_3$ to $Pd(OAc)_2$ yields of 3CC product could be increased 3-fold with a significant improvement in the ratio of 3CC:phenanthrene (Entry 4, Table 2.2). It could be hypothesised that the dba ligands are not being fully displaced by phosphine, and that their coordination inhibits the reaction with acrylate.[9] The screen did not show any improvement over the bidentate dppe ligand, with similar ligands such as dppp dropping the yields of 3CC to almost zero (Entry 5, Table 2.2). Using these improved catalyst conditions further changes were made to the system. The temperature was altered to room temperature and to 80 °C, the former yielding only phenanthrene and the latter giving a complex mixture with no product evident. The amount of CsF used was reduced from 4 to 2 equivalents, however this dropped the yield to 17%. Additional bases were also considered; K_2CO_3, Cs_2CO_3 and tetrabutylammonium acetate all having a negative effect on the reaction, possibly due to altering the solubility of CsF. Finally, altering the ratios of reactants by doubling the number of equivalents of either allyl chloride or methyl acrylate did not yield improved results.

It was thought that phenanthrene formation could be limited by reducing the concentration of benzyne in the reaction, the reactive aryl-palladium species formed *in situ* then having less chance of reacting with benzyne before it could be intercepted by the acrylate. The solvent, temperature and fluoride source could all be controlled in order to slow the rate of benzyne generation. As Yamamoto successfully used solvent to control benzyne generation rate, causing a switch in the product observed, this seemed to be a suitable starting point for further investigation.[106]

Table 2.3 Solvent screen for three component Heck coupling

Entry	Solvent(s)	Solvent Ratio	3CC (89) %
1	MeCN		28
2	MeCN/DCM	1:1	24
3	MeCN/THF	1:1	0
4	MeCN/Toluene	1:1	14[a]
5	DMF		0
6	DME		50
7	1,4-dioxane		Starting material
8	MeCN/1,4-dioxane	1:2	35[b]
9	DME/1,4-dioxane	1:1	Starting material
10	DCE		Starting material

Reactions were carried out using a 1:1.2:2.4 ratio of **1**:**87**:**88** with 5%Pd/ligand and CsF 4equiv in MeCN at 50 °C for 24 hrs. [a]36% benzyne precursor **1** recovered. [b] MeCN added slowly over 6 hours.

Over a wide range of solvents, two particularly promising results were achieved. The first was using a mixture of MeCN with 1,4-dioxane, no phenanthrene being formed if the MeCN is added slowly, over extended periods of time. After considerable optimisation of the solvent ratio, rate of addition and reaction time a maximum yield of 35% was achieved (Entry 8, Table 2.3). Although this solvent mixture yields excellent selectivity for three component Heck coupling over the benzyne-benzyne-allyl reaction, the procedure itself is lengthy and time-consuming as many small additions of MeCN are required for optimal yield. In order to avoid the need for slow addition of MeCN, 18-crown-6 was added to the reaction in dioxane, however this either gave large amounts of phenanthrene (0.5 equiv. 18-crown-6) or left significant quantities of starting material remaining (0.1 equiv. 18-crown-6). Pleasingly, a switch from MeCN to 1,2-dimethoxyethane (DME) improved the yield from 28% to 50%, with 33% phenanthrene also isolated (Entry 6,

Table 2.3 2.3). This is probably due to the slower rate of benzyne formation in this solvent, as CsF is around 10-fold less soluble in DME than in MeCN.[144]

Table 2.4 Screen of bidentate phosphine ligands

Entry	Pd Source	Phosphine	3CC (89) %
1	$Pd(OAc)_2$	dppe	50
2	$Pd(OAc)_2$	dppp	0[a]
3	$Pd_2(dba)_3$	dppb	41
4	$Pd(OAc)_2$	dppm	0[a]
5	$Pd(OAc)_2$	dpppent	0[a]
6	$Pd(OAc)_2$	dpphex	0[a]
7	$Pd(OAc)_2$	XANTPHOS	Exclusively phenanthrene
8	$Pd(OAc)_2$	dppb	0
9	$Pd_2(dba)_3$	dppe	30
10	$Pd(dppf).Cl_2$	-	21[b]
11	$Pd(OAc)_2$	dppe	37[c]
12	$Pd(OAc)_2$	dppe	39[d]

Reactions were carried out using a 1:1.2:2.4 ratio of **1**:**87**:**88** with 5%Pd/ligand and CsF 4equiv in 1 mL DME at 50 °C for 24 hrs. [a] Mainly phenanthrene. [b] 56% phenanthrene isolated. [c] 3 mL solvent used. [d] 80 °C.

With this result in hand a second catalyst screen was performed, focussing on bidentate ligands. The reaction remains particularly sensitive to the ligand employed, with dppe and dppb giving the only successful reactions (Entries 1 and 3, Table 2.4). Alternative temperatures were again tried, 80 °C giving a 39% yield of **89** with increased levels of phenanthrene, in all probability due to the increased solubility of CsF. A reaction at higher dilution was also performed, giving a drop in yield to 37%, for a similar reason.

One of the problems with the reaction, particularly when DME was used as a solvent, was a lack of reproducibility. Lower yields appeared to collate with poor mass recovery after reaction work-up, which may be due to water in the reaction causing formation of phenol. As solvents were being rigorously dried by distillation over

sodium, and used immediately, the problem was most likely due to cesium fluroride, which is highly hygroscopic. During initial investigations this had been used as supplied, direct from the bottle. Either drying this reagent under vacuum at 100 °C overnight prior to use or flame drying immediately before the reaction yielded poor results, with significant quantities of benzyne precursor (**1**) remaining, even when the amount of CsF used was increased from 3 to 6 equivalents. A similar result was seen using molecular sieves in the reaction. These results suggest both that it is likely some benzyne is being consumed as phenol, and also that a small quantity of water is required to aid dissolution of the cesium fluoride and hence benzyne generation.

Table 2.5 Screen of alternate fluoride sources

Entry	Fluoride source	Solvent	3CC (89) %	Phenanthene (90) %
1	KF/18-crown-6	THF	0	23
2	TBAF	MeCN	0	mainly phenanthrene
3	KF/alumina	MeCN	0	starting material
4	RbF	MeCN	0	starting material
5	RbF	DME	0	starting material
6[a]	RbF	DME	1:1 sm:prod	

Reactions were carried out using a 1:1.2:2.4 ratio of **1**:**87**:**88** with 5%$Pd(OAc)_2$/dppe and CsF 4equiv in 1 mL solvent at 50 °C for 24 hrs**.** [a] Reaction temperature 80 °C.

A selection of fluoride sources were also considered as an alternative to changing solvent, however neither different inorganic nor organic fluorides yielded a suitable increase in the yield of 3CC product (Table 2.5). RbF, although producing little 3CC at 50 °C (ratio of 45:1 starting material **1**:product **89** by NMR), did yield a 1:1 ratio of **1**:**89** when heated overnight at 80 °C in DME, without any evidence of phenanthrene formation (Entries 5 and 6, Table 2.5). Although not followed up at the time, this may have supplied a suitable alternative to CsF in this reaction.

Microwave heating was also considered, as this has been widely reported to significantly increase the rate of palladium catalysed reactions.[145] It was found, however, that using either dioxane or DME as solvent over a range of temperatures (120-190 °C) and times (20-30 mins.) benzyne precursor (**1**) was recovered

unchanged, with only small traces of 3CC product **89**. This may be due to insufficient stirring caused by the quantity of cesium fluoride in the reactions, cesium fluoride being insufficiently dissolved or the time period for benzyne formation not being sufficiently long.

Finally, alternative allyl sources, namely the bromide and acetate, were also utilised in the reaction, as different halide ions at palladium are known to confer a change in reactivity.[146] This, however, was unsuccessful, with desired 3CC product not being observed with either substrate.

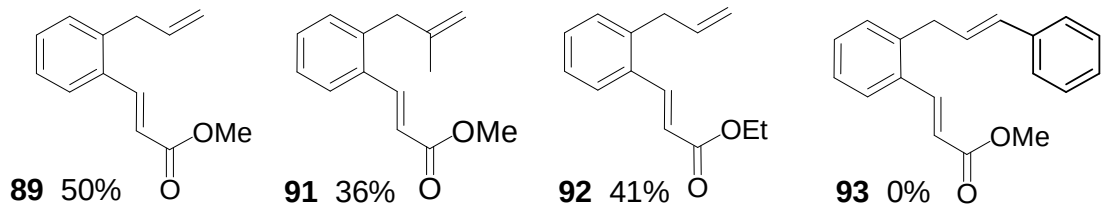


Figure 2.7 Products from three component allyl Heck reaction

Utilising the optimised conditions (Entry 1, Table 2.4) a small variety of different allyl chlorides and acrylates could be employed in the 3CC to give the compounds depicted in Figure 2.7. The conditions were not robust, giving inconsistent yields which were generally low. A wide range of allyl chlorides were not suitable for the reaction as evidenced by the lack of product **93** when using cinnamyl chloride.

Whilst not wishing to move away from π-allyl type systems, it was clear that an alternative to allyl chlorides was required. Two systems that could not undergo phenanthrene formation whilst still forming the key palladium- π-system would be α-bromo ketones and benzyl halides, and the use of these in three component coupling will be discussed in the subsequent section.

2.2.2 Unforseen issues

The problem with the Heck reaction of allyl chlorides, in comparison to their successful use in both Stille and Suzuki reactions is initially surprising but could be explained in a number of ways. It has not been possible to improve the yield of three component coupling, even though a Heck reaction with the arylpalladium species generated should be fast under the reaction conditions. This may be due to the double bond of the allyl species coordinating palladium to form a cyclic complex (**96**), preventing coordination of the acrylate group. If this occurs the only outcome would be phenanthrene, formed via the pathway illustrated in Figure 2.8. The increased yield seen by altering solvent and ligand system could then be attributed to a slower rate of benzyne generation, in the first instance, or steric hindrance from either phosphine ligand or interaction of solvent not allowing strong coordination of the allyl double bond to palladium. The coordination of the allyl group is reversible (**95** to **96**) thus it cannot completely suppress formation of the 3CC product **99,** however it would strongly favour the formation of phenanthrene **90** in preference to undergoing three component Heck reaction.

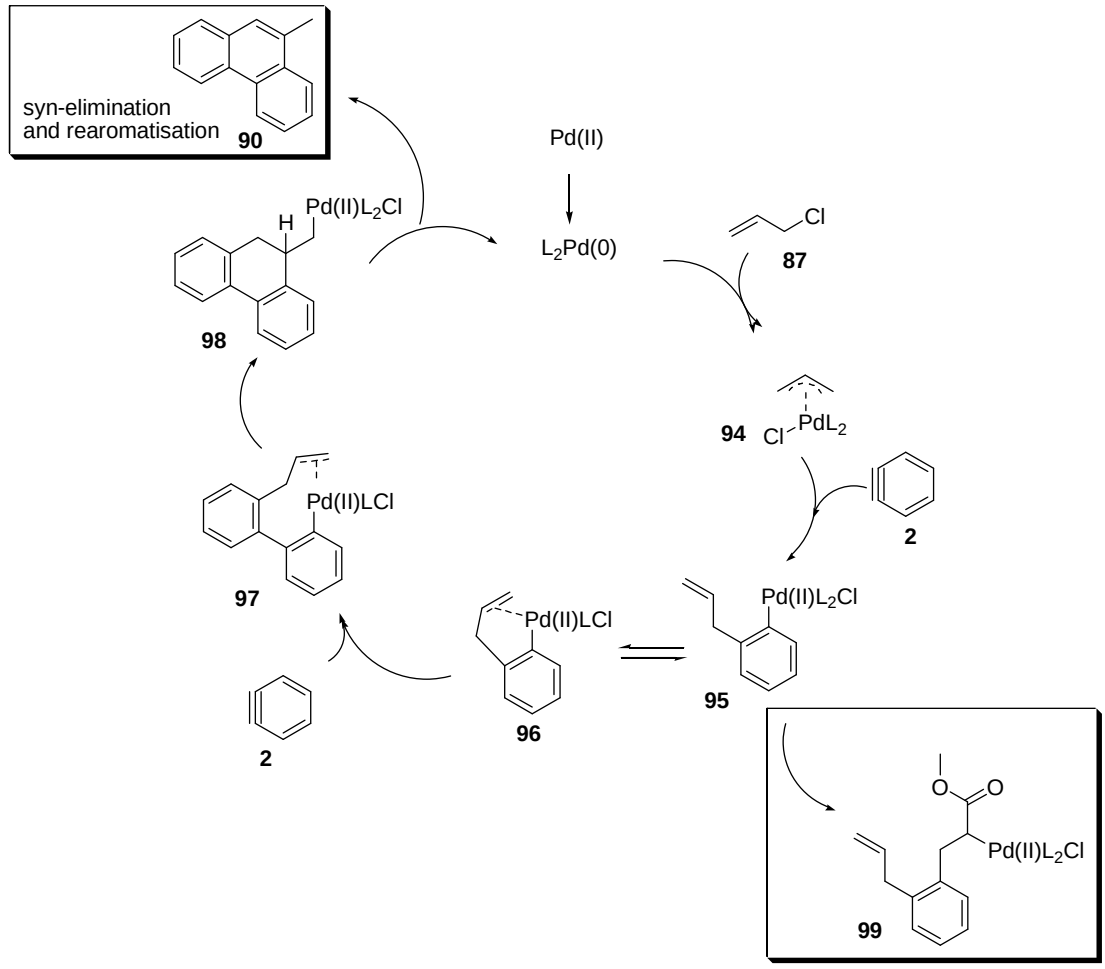


Figure 2.8 Possible mechanistic pathway for three-component allyl chloride-benzyne-acrylate Heck reaction

Success achieved in the Stille and Suzuki reactions could then be attributed to the transmetallation step taking place despite the coordination of the allyl group, allowing a successful coupling in these cases. During transmetallation, unlike syn-addition, the halide is replaced by the R-group from the organometallic. Coordination of the allyl group to palladium, followed by syn-addition, could facilitate formation of the 6-5 indene **103** or 6-4 benzocyclobutene **101** system, neither of which is observed. Such a reaction has not been reported, however, and may be disfavoured due to steric reasons or ring strain. Addition of palladium to the favoured, less substituted end of the double bond would lead to formation of a four-membered ring **100**, whereas five-membered ring formation would put the palladium into a highly sterically-crowded environment **102** (Figure 2.9). Indeed the Heck

reaction can be successfully employed to form 3- to 9-membered rings, however some restrictions apply; where a 5-membered ring or smaller is formed these are only accessible by n-exo processes, giving initially the exocyclic double bond. Looking to the literature, where 1-allyl-2-iodobenzene for example has been used in palladium catalysed reactions, cyclisation of this species has not been reported.

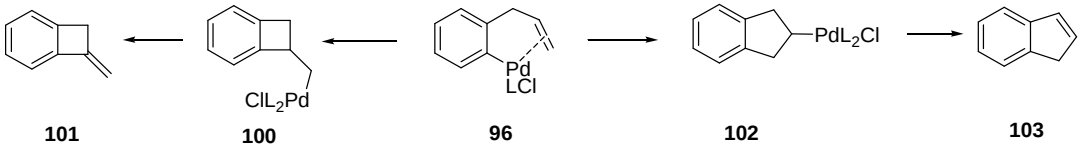


Figure 2.9 Formation of bicyclic structures through Heck reaction of 2-allylarylpalladium species

The second possibility is that in the case of the Stille and Suzuki reactions, transmetallation (**105**) occurs prior to carbopalladation of benzyne, reductive elimination then being slow enough to allow reaction with benzyne to furnish the 3CC product **106** (Figure 2.10). This mechanism is less likely, although should not be completely discounted. Thirdly, an aryl stannane may be formed through palladium catalysed carbometallation, which then undergoes a two component Stille reaction to yield the 3CC product (Figure 1.57).[117]

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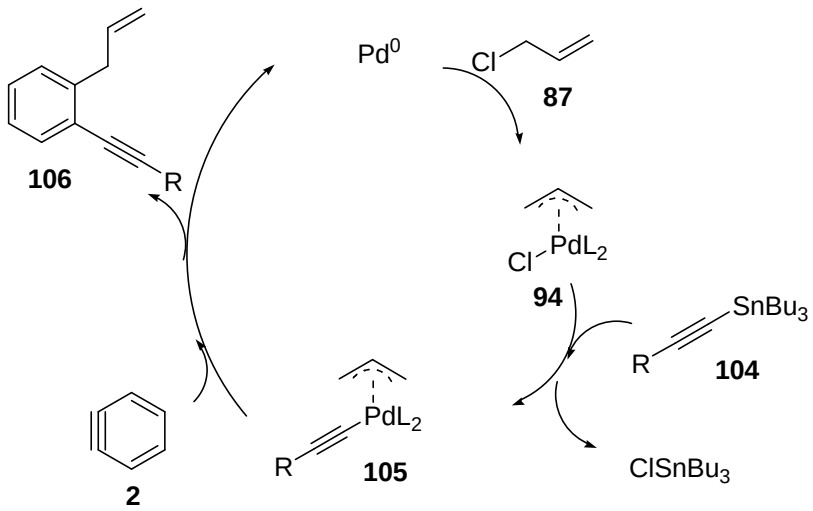


Figure 2.10 Proposed mechanism involving transmetallation to palladium prior to involvement of benzyne

2.3 α-Bromo acetates

Due to the 3CC of allyl chlorides being low yielding, an alternative electrophile that would circumvent phenanthrene formation was sought. α-Haloketones or esters can form the desired π-system after oxidative addition to palladium, retaining the necessary stability associated with π-palladium intermediates. It has been speculated that reacting π-systems with benzyne should be more straightforward than the more unstable aryl-palladium systems as in the latter case the meeting of two reactive, transient species is required for a successful reaction. Similar to the allyl chlorides, these species have also not been previously utilised in two component Heck couplings, so again it should be possible to achieve excellent selectivity for two *vs* three component coupling.

2.3.1 Reaction optimisation

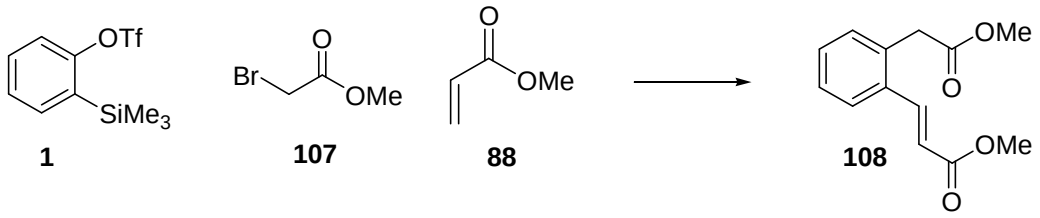
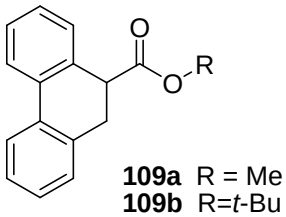


Figure 2.11 Three component coupling of bromomethylacetate **107** with benzyne **1** and methyl acrylate **88**

Initial studies directed towards the three component coupling used α-bromomethylacetate (**107**) as a replacement for the allyl chloride and yielded immediate success (Figure 2.11). When the optimised conditions for the allyl chloride coupling were applied, namely CsF in DME at 50 °C for 24 hours, 31% of three component coupling product **108** was isolated (Entry 1, Table 2.6). However, it wasn't possible to escape from problems with the formation of multi-benzyne containing products. In this instance the product was formed from the reaction of two benzyne molecules with methyl acrylate forming methyl 9,10-dihydrophenanthrene-9-carboxylate **109a** in 52% yield (Figure 2.12). The side-product probably forms via sequential addition of benzyne to palladium, possibly yielding the cyclic intermediate **112** (Figure 2.13). Support for such an intermediate

comes from the work of Wenger *et. al*. who found that during their attempts to isolate η_2-palladium-benzyne species, either dimeric palladium species or cyclic intermediates such as **112** were formed.[147] This biphenyl palladium species would then coordinate the acrylate and undergo syn-addition to give a second cyclic species **114**. Reductive elimination from this species gives the observed phenanthrene **109a**, whereas β-hydrogen elimination yields an arylpalladium species (**115**) which could react with a second equivalent of acrylate but is more likely to undergo intramolecular addition to again yield **114**. A second possible mechanism exists whereby a cyclic species is formed through interception of the benzyne by alkene (**113**), reminiscent of the nickelacycle proposed by Cheng.[127] This cyclic species would then be intercepted by benzyne, yielding **114**, the catalytic cycle then continuing as previously. Formation of didehydrophenanthrenes along with other benzyne-benzyne-alkene products has subsequently been reported.[108] The other product observed by Guitian and co-workers was *ortho*-olefinated biaryl from reductive elimination of palladium-hydride species **115**, which was not observed as a by-product during this work.



109a R = Me
109b R=*t*-Bu

Figure 2.12 9,10-dihydrophenanthrene-9-carboxylate esters are formed from reaction of 2 equiv. benzyne with the alkene

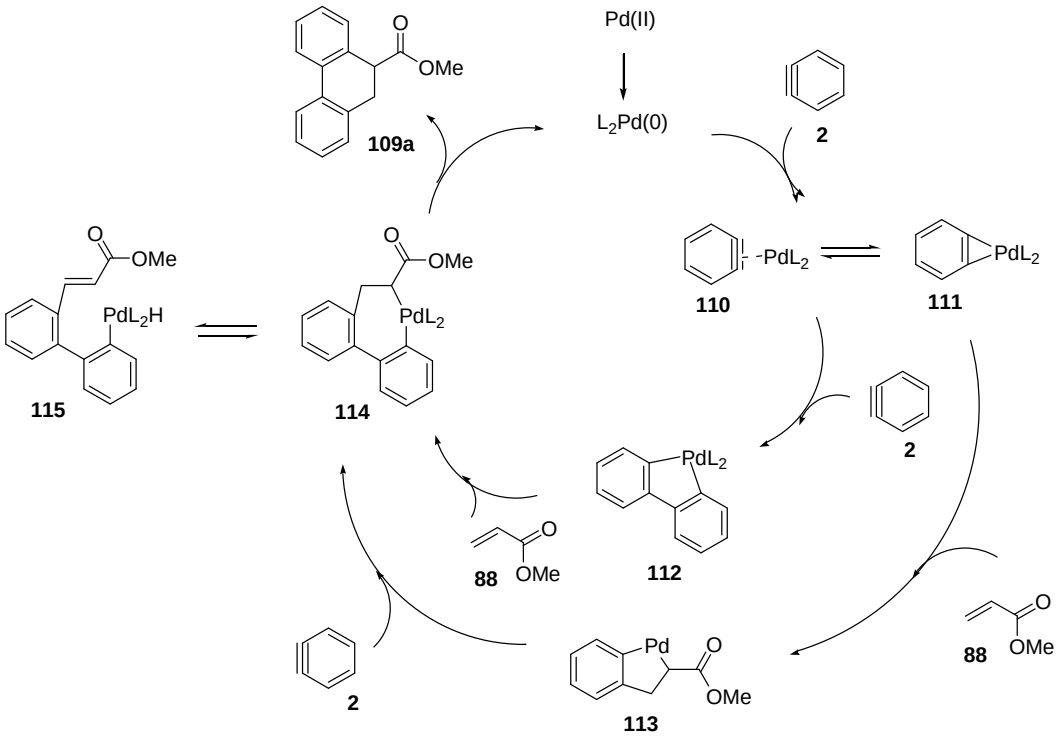


Figure 2.13 Mechanism of dihydrophenanthrene formation

To improve on the initial positive result, a screen of palladium sources and phosphine ligands was undertaken. This showed promise for increasing the yield of the reaction, with Pd(0) sources initially proving optimum, both $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ giving increased yields (Entries 4 and 5, Table 2.6). The optimum catalyst system was found to be $Pd(dppf).Cl_2$ (Entry 11, Table 2.6), which gave a very clean reaction with minimal evidence of dihydrophenanthrene **109a** being formed. In contrast to the reaction with allyl chlorides it was found that a small excess of benzyne was beneficial to the reaction - bromomethylacetate **107** being the stoichiometric reagent. However, a successful reaction could also be achieved using only one equivalent of benzyne precursor and 1.2 equivalents of methyl acrylate **88**, reducing the yield from 75% to 62% (Entry 13, Table 2.6) with $Pd(dppf).Cl_2$, although the yield decreased by a much smaller margin, from 60% to 58% when $Pd_2(dba)_3$/dppb was used as a catalyst system. Indeed for various systems a clear pattern could not be discerned in relation to changes in yield when going using benzyne **1** in excess or as the stoichiometric reagent. Addition of further equivalents of phosphine ligands to the reaction proved deleterious, reducing the yield to 49%

(Entry 14, Table 2.6). CsF could be increased up to 6 equivalents (c.f. benzyne) without any significant effect on yield, an advantage as hygroscopic CsF can be added directly to the reaction vessel, without the need for accurate weighing. Scaling up of the reactions was also possible, giving only a small change in yield.

Table 2.6 Screen of catalyst systems for three component coupling of bromomethylacetate

Entry	Palladium Source	Phosphine	Yield (108) %
1[a]	$Pd(OAc)_2$	dppe	31
2[a]	$Pd(OAc)_2$	dppb	42
3	$Pd(dppe)_2$	-	32
4	$Pd(PPh_3)_4$	-	51
5[a]	$Pd_2(dba)_3$	dppe	44
6	$Pd_2(dba)_3$	dppp	65
7	$Pd_2(dba)_3$	dppb	60
8[a]	$Pd_2(dba)_3$	dppb	58
9	$Pd_2(dba)_3$	dpppent	60
10[a]	$Pd_2(dba)_3$	dpphex	29
11	$Pd_2(dba)_3$	dppm	Complex mix
12	$Pd(dppf).Cl_2$	-	75
13	$Pd_2(dba)_3$	dppf	Complex mix
14[a]	$Pd(dppf).Cl_2$	-	62
15	$Pd(dppf).Cl_2$	dppf	49

Reactions were carried out using a 1.5:1:1.5 ratio of **1**:**107**:**88** with 5%Pd/ligand and CsF 4equiv in DME at 50 °C for 24 hrs. [a]Ratio of reactants used 1:1:1.2

Despite the discovery of a successful set of reaction conditions it was felt necessary to investigate a range of other parameters to ensure that the optimum conditions had been found. Reaction in MeCN yielded exclusively triphenylene, formed from the trimerisation of benzyne. Alternative fluoride sources were also considered, however neither TBAF nor tetrabutylammonium triphenyl difluorosilicate (TBAST) generated benzyne under the reaction conditions. Changing to the 2-(*tert*-butyldimethylsilyl)phenyl trifluoromethanesulfonate **116** (Figure 2.14), a benzyne precursor with a bulkier silyl group, gave no yield in either MeCN or DME, 97%

starting material being recovered although this precursor has previously been reported to generate benzyne.[56] A more complete investigation of alternatives to both silyl and triflate groups was not undertaken as aspects of this work have been previously reported with little success.

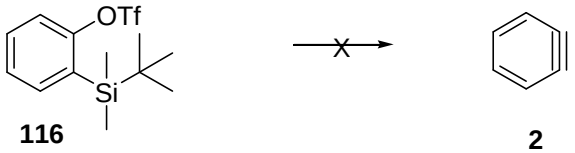


Figure 2.14 2-(*tert*-Butyldimethylsilyl)phenyl trifluoromethanesulfonate was not a suitable benzyne precursor

2.3.2 Results

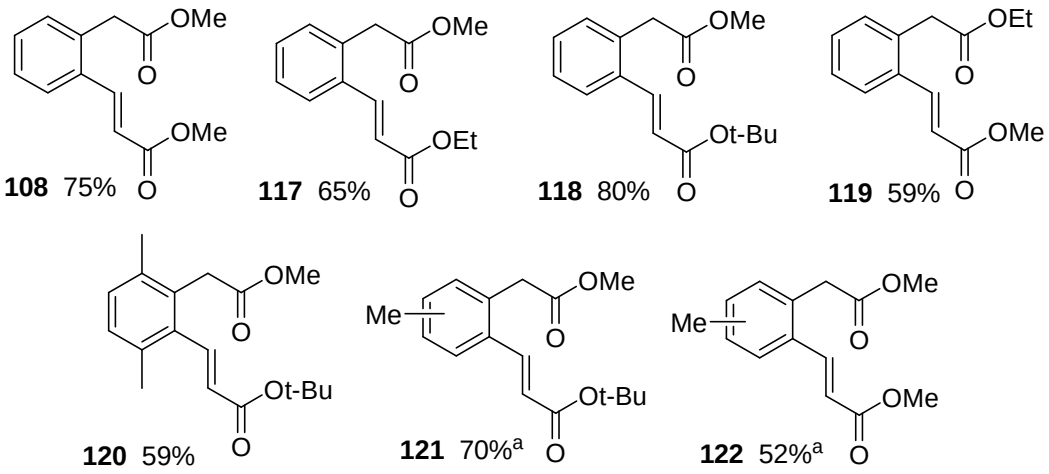


Figure 2.15 Various bromoacetates and acrylates could be used in the reaction. [a]Isolated as a 50:50 mixture of two regioisomers

Utilising the optimised reaction conditions commercially available acrylates and bromoacetates were employed in the 3CC, giving good yields of the coupled products. Substituted benzyne precursors could be used, generating poly-substituted aromatics, such as **120** (Figure 2.15). Where the benzyne precursor was unsymmetrically substituted a mixture of regioisomers was observed **121** and **122**. This helps demonstrate the intermediacy of benzyne in the reaction, which will be discussed in more detail later in this chapter. Unfortunately the reaction conditions could not be simply extended to involve a range of alkenes, commonly employed in

the Heck reaction (Figure 2.16). It is unclear why 3CC has been unsuccessful in this case; it is possible that the desired 3CC products are formed but are difficult to separate from the unreacted starting materials or multi-benzyne containing by-products. Another possibility is that more reactive alkenes may undergo a larger proportion of non-catalysed reactions with benzyne, or have a tendency to undergo [2+2+2] benzyne-benzyne-alkene cyclisation. It is clear, however, from NMR and TLC of the crude reactions that the outcome is not trivial, often benzyne being consumed by trimerisation to triphenylene.

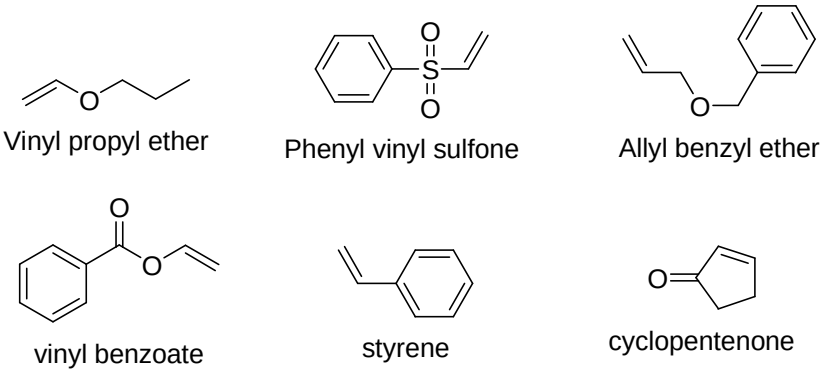


Figure 2.16 Alkenes which were unsuccessful in the 3CC reaction

2.3.3 α-Halo ketones

After developing this chemistry using bromomethylacetate, attempts to expand the reaction to a range of α-halo carbonyl species was made. Amongst these, the α-halo acetophenones are particularly interesting as 3CC would form an appealing structural motif.

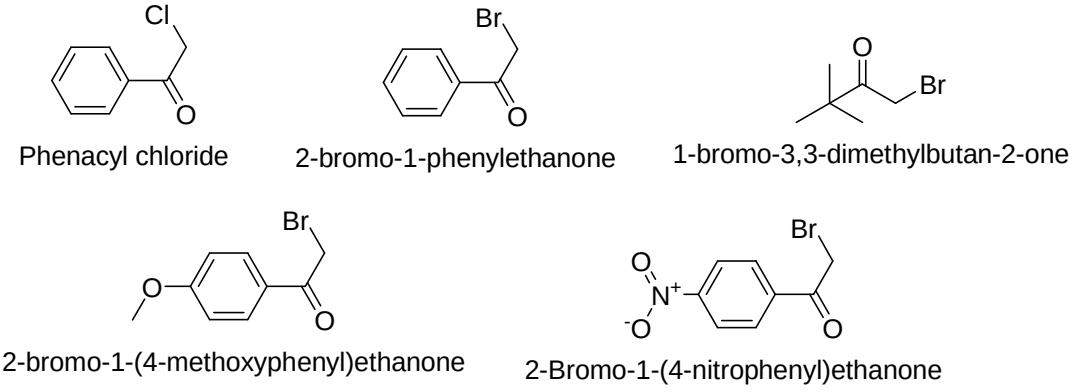
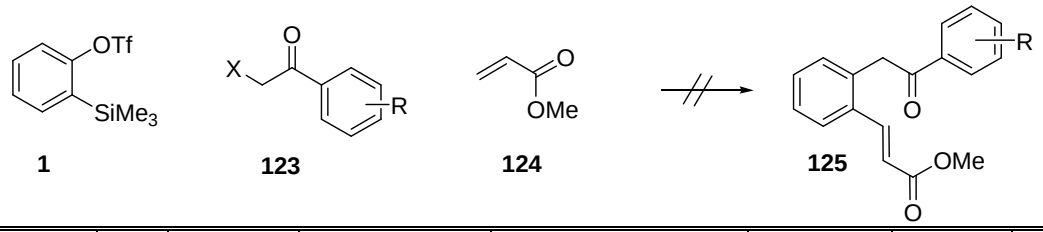


Figure 2.17 Alternative α-bromo ketones

Despite some screening no reaction using a variety of electron poor and electron rich α-bromoacetophenones or alkyl derivatives was achieved (Figure 2.17), unchanged organohalide or proto-debrominated products generally being observed by NMR. Upon searching the literature it seems there are limited reports of using these species in palladium coupling reactions; the scant mentions of these concerning their use in carbonylation.[148] Also, the related α-bromo sulfoxides have been employed successfully in the Suzuki reaction.[149] This could possibly be due to an unexpectedly slow rate of oxidative addition or could be caused by the intermediate palladium species being particularly stable, effectively poisoning the catalyst. In an attempt to speed the rate of oxidative addition NaI was also added to the reactions, which should undergo a Finkelstein reaction to form the more reactive alkyl iodides *in situ*. Unfortunately this did not change the course of the reaction, supporting the theory that the palladium species is unusually stable towards further reaction. Indeed, similar species have been used as additives to promote homocoupling of boronic acids and organozinc species through cleavage of the Pd-oxygen (η^1) enolate, discussed further in Section 2.8.

Table 2.7 Conditions screened for 3CC using α-haloacetophenones



1 **123** **124** **125**

Entry	X	R	Pd source	Ligand	Solvent	Temp	Time
1	Br	H	$Pd_2(dba)_3$	dppb	DME	50 °C	o/n
2	Br	H	$Pd_2(dba)_3$	dppp	DME	50 °C	o/n
3	Br	H	$Pd(dppf).Cl_2$		DME	50 °C	o/n
4	Br	H	$Pd(dppf).Cl_2$		DME	70 °C	o/n
5	Br	4-OMe	$Pd(dppf).Cl_2$		DME	50 °C	o/n
6	Br	4-NO_2	$Pd(dppf).Cl_2$		DME	50 °C	o/n
7	Cl	H	$Pd(dppf).Cl_2$		DME	50 °C	o/n
8	Cl	H	$Pd(dppf).Cl_2$		DME	50 °C	o/n
9	Br	4-Cl	$Pd(OAc)_2$	P(*t*-Bu)$_3$.HBF_4	MeCN	50 °C	4 hrs
10[a]	Br	4-Cl	$Pd(OAc)_2$	P(*o*-tol)$_3$	MeCN	50 °C	4 hrs
11[a]	Br	4-OMe	$Pd(OAc)_2$	P(*o*-tol)$_3$	MeCN	50 °C	4 hrs

Reactions were carried out on a 0.2 mmol scale with 5 mol% Pd, 3 equiv CsF and a 1:1:1.2 ratio of **1:123:124** in 1 mL solvent. [a] 1 equiv. NaI added. [b] 1:1.5:1 ratio of **1:123:124**

The reaction conditions screened are shown in Table 2.7. Conditions mirroring those successful for the coupling of α-haloesters were employed with various substrates without success. A wide screen of other catalyst systems, solvents, temperatures and additives was not undertaken, due to the lack of literature on the use of these substrates in coupling reactions.

2.4 Benzyl Halides

A second alternative to allyl chlorides would be the use of benzyl halides to form the desired Pd-π species. Such a reaction is particularly attractive as a wide range of substituted benzyl halides and heteroaryl derivatives are commercially available, promising the possibility that structural diversity could be rapidly incorporated.

2.4.1 Reaction development

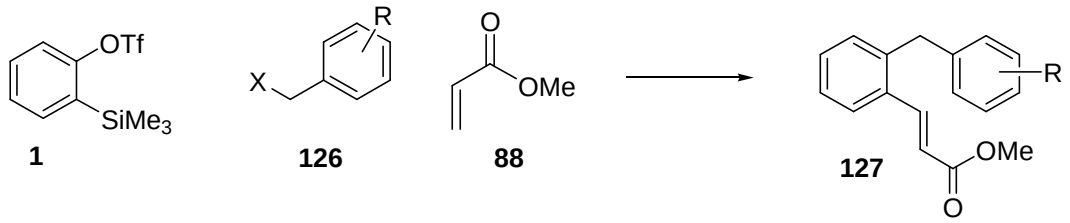
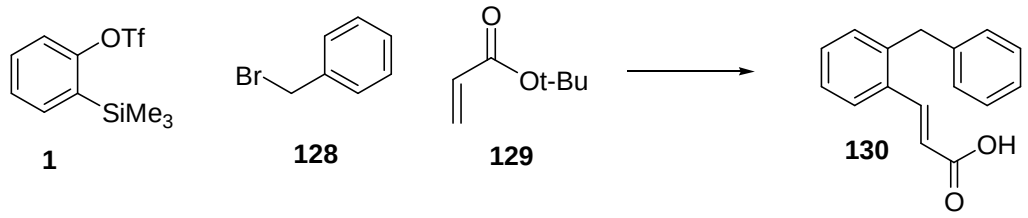


Figure 2.18 Proposed three component coupling of a benzyl halide with benzyne and acrylate

Initial studies were conducted with benzyl chloride, however only very small amounts of 3CC was observed using a variety of catalyst systems, with unreacted benzyl chloride and benzyne-benzyne-alkene coupling product **109a** being the major species by NMR. Benzyl bromide **128**, however, yielded a more promising reaction (Figure 2.18). In this case, using conditions as per bromomethylacetate, a successful coupling was achieved. Again, dihydrophenthrene **109a** was produced in the reaction which caused purification issues, with the desired compound being isolated as a 1:1 mixture. By utilising the benzyl bromide as the reactant in excess, the amount of unwanted benzyne-benzyne-alkene product **109a** could be reduced, however silica chromatography continued to yield a mixture of products thus an alternative to chromatography was also sought. By cleaving the ester group, simply achieved by stirring the crude reaction with TFA/DCM at room temperature (where *t*-butyl acrylate was used), the products could be purified from by-products and excess benzyl bromide via trituration or recrystallisation. A screen of catalyst systems showed that a good increase in yield with concomitant decrease in benzyne-benzyne-alkene product **109b** could be achieved by returning to $Pd(OAc)_2$/dppe (Entry 2, Table 2.8). In fact, applying this system to the reaction between *t*-butyl acrylate and benzyne **1** produced exclusively triphenylene, with no evidence of benzyne-benzyne-alkene coupling **109b**. It is also interesting to note that no 2CC between benzyl bromide **128** and acrylate **129** was observed during the optimisation; indeed when the reaction was conducted in the absence of benzyne, benzyl bromide was recovered unchanged.

Table 2.8 Optimisation of catalyst system for 3CC of benzyl bromide with benzyne and *t*-butyl acrylate



1 **128** **129** **130**

Entry	Palladium Source	Ligand	Yield (130) %
1[a]	$Pd(dppf).Cl_2$		1:1 mix with **109b**
2	$Pd(OAc)_2$	dppe	65%
3	$Pd_2(dba)_3$	dppe	47%
4	$Pd(OAc)_2$	dppb	24%
5	$Pd(OAc)_2$	dppp	Complex mix
6	$Pd(OAc)_2$	XANTPHOS	0%
7	$Pd(PPh_3)_4$		Complex mix

Reactions were carried out using a 1:1.5:1 ratio of **1:128:129** with 5%Pd/ligand and CsF (4equiv.) in DME at 50 °C for 24 hrs, followed by ester hydrolysis using TFA/DCM. [a]Isolated as the ester

As observed previously, alteration of the reaction temperature had a detrimental effect on the reaction, with a drop in yield from 76% to 43% and 38% respectively when room temperature or 80 ºC was used. In contrast to the bromoacetates, MeCN could be employed as solvent, however this again dropped the yield to 27%. Catalyst loading could be reduced to 1 mol%; however this did decrease the yield from 76% to 42%. As the reactions are being conducted on a small scale, employing just 2 mg of palladium catalyst, such a drop in loading may have a smaller effect if the reactions were being conducted on a larger scale. A reaction at higher dilution, using 15 mL solvent, did not yield any success, giving a complex mixture of products, probably due to the change in benzyne generation rate.

2.4.2 Results

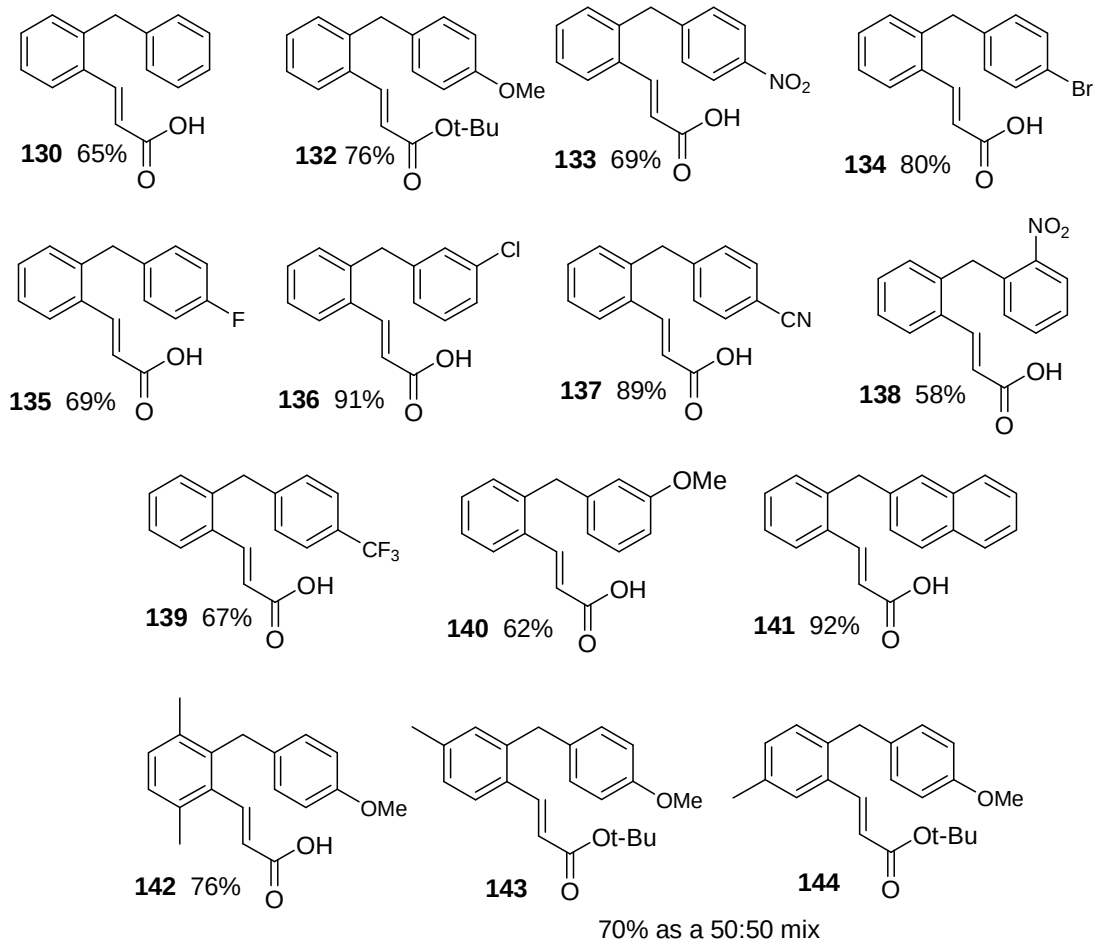


Figure 2.19 3CC products synthesised from reaction of aryl bromides with aryne and *t*-butyl acrylate, followed by acidic cleavage of the ester group using TFA (where necessary)

Both the reaction conditions and purification techniques were applicable to a wide range of benzyl bromides (Figure 2.19). Electron withdrawing and donating substituents were equally well tolerated, and substitution could be in *ortho*-, *meta*- or *para*- position. Aryl halides, in particular bromide substituents, were unreactive towards the palladium catalyst using these conditions, with no second Heck reaction being observed. This produces products that contain a handle for further elaboration by a second palladium cross-coupling reaction. Other functional groups such as nitro- and cyano- could also be incorporated, which allow further elaboration to the aniline, amide or amine.

Heteroaryl derivatives were not well tolerated, however. In particular the bromomethylpyridines yielded black tars which streak on TLC, probably due to polymeric products being formed. Polymerisation reactions of benzyne and pyridines have been previously reported.[150] 2-(Bromomethyl)-5-nitrofuran was also used as a reactant and unsurprisingly did not yield any of the desired 3CC, a Diels-Alder reaction presumably consuming the benzyne more rapidly than its reaction with palladium. Substituted benzyne precursors could be used, in particular the 2,6-dimethyl substituted benzyne giving a successful reaction despite the arene formed being highly substituted, **142**. An equal mixture of regioisomers (**143** and **144**) was formed using an unsymmetrically substituted benzyne precursor, again demonstrating that a free aryne species is likely to take part in the reaction. Reactions with other alkenes were attempted but, as previously, did not yield any of the desired products. The optimised conditions were also applied to alkyl bromides lacking β-hydrogens, however this was again unsuccessful.

2.5 Mechanistic considerations

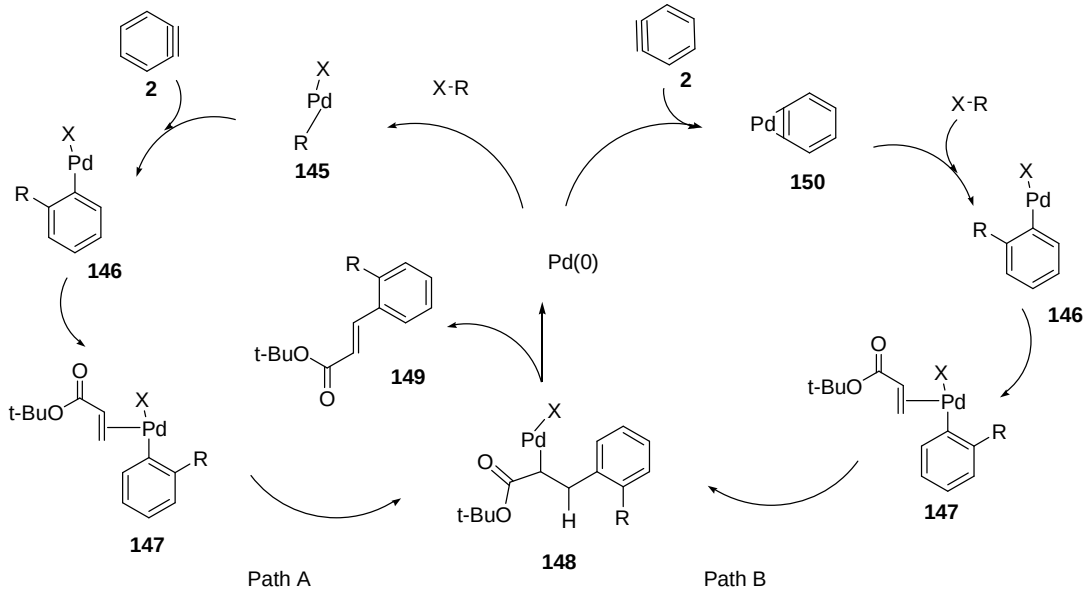


Figure 2.20 Two possible mechanistic pathways for three component coupling

When discussing the mechanism of these reactions, two possible pathways could be considered. These differ, primarily, in the opening steps of the catalytic reaction; either beginning with the oxidative addition of the organohalide to the palladium catalyst (**145**), which would be conventionally thought of to be the first step in palladium catalysed reactions or with coordination of benzyne to the palladium species (**150**), which would then be followed by the oxidative addition of the organohalide to the palladium-benzyne complex (Figure 2.20). This second mechanism is difficult to prove as a true palladium-benzyne complex has never been successfully generated, the reported systems tending to dimerise, as previously mentioned.[147] The former of these two mechanisms (Path A) involves a bimolecular reaction between two reactive intermediates, namely the organo-palladium species **146** and benzyne. This mechanism could be disproved if reaction of a preformed organo-palladium species, in a stoichiometric quantity, fails to react with benzyne and acrylate to yield the desired 3CC product (**149**). To this end, the reaction with commercially available transbenzyl(chloro)bis(triphenylphosphine) palladium(II) **150** was undertaken under similar conditions to the previous reactions (Figure 2.21). The 3CC product was isolated in a yield of 40% after several rounds of purification to remove the significant quantities of triphenylphosphine oxide generated. Although the yield is lower than in the catalytic reaction this goes some way to show that the former mechanism, where oxidative addition is the first step in the catalytic cycle, could be in operation in this case. It is not possible from this result to rule out either mechanism; theoretically the palladium species could reductively eliminate benzyl chloride, thus being able to begin the reaction sequence by addition of benzyne. This is highly unlikely, however, as previous results have shown little propensity of benzyl chloride to participate in 3CC reactions.

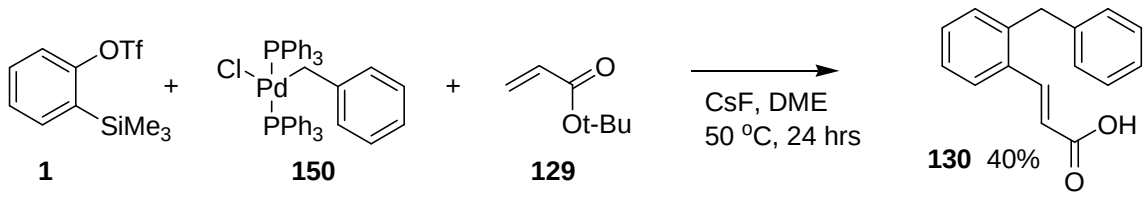


Figure 2.21 3CC using a stoichiometric organopalladium reagent

2.6 Benzyne as an intermediate

One very important question that needs to be addressed is whether or not free benzyne is involved in the reaction. For example, it is possible for the triflate to oxidatively add to palladium and undergo a two component Heck coupling. The silyl portion could also take part in a Hiyama reaction, yielding 3CC product without benzyne being formed (Figure 2.22). Indeed, in Yamamoto's early work involving reaction of benzyne with alkynes he found some instances where oxidative addition of triflate occurred in preference to formation of free benzyne.[106]

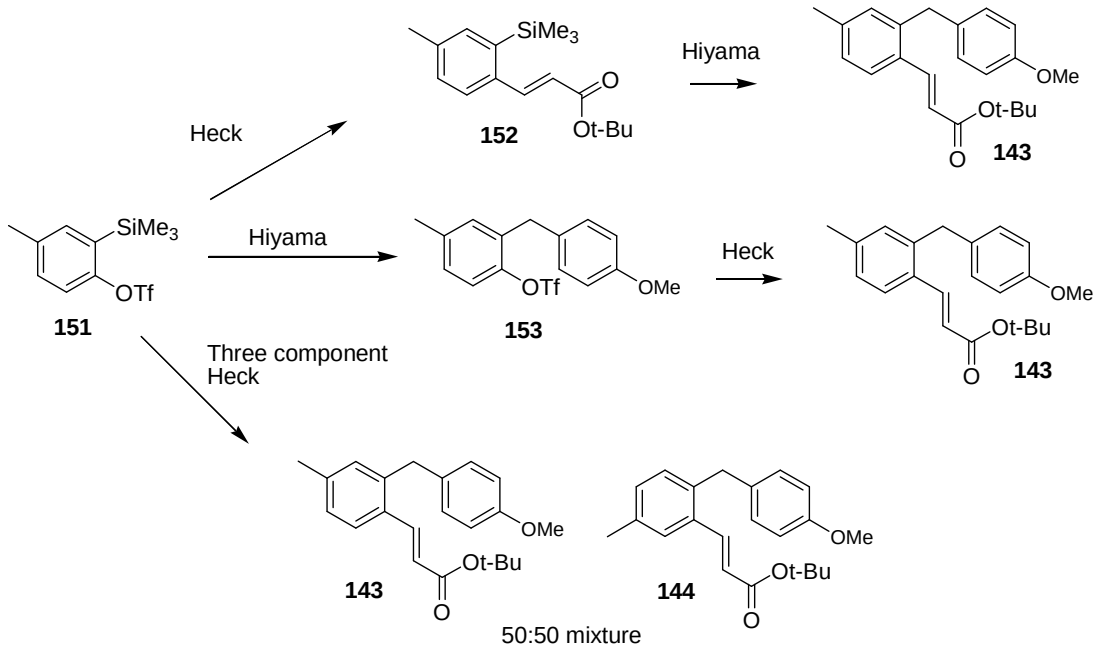


Figure 2.22 Alternate reaction mechanisms for 3CC not involving benzyne

Control experiments where no fluoride source was used did not give a reaction, NMR of the crude reaction mixture showing unreacted starting materials as the sole components. This suggests that the aryltriflate does not undergo oxidative addition to palladium under the reaction conditions. Additionally, the use of an unsymmetrically substituted benzyne precursor **151** lends further support for the involvement of benzyne in the reaction. Were a sequential series of palladium couplings to occur only one of the two regioisomers would be observed where the acrylate group lies *para* to the methyl. The observed products are isolated as a 1:1

mixture of the two regioisomers (**143** and **144**), thus free benzyne is probably participating in the reaction (Figure 2.22).

2.7 Applying the methodology

During the development of a novel synthetic methodology it is important that it can be applied to the synthesis of useful or interesting compounds, which may be difficult or time-consuming to produce using existing methods. To this end these three component benzyne couplings could be applied to the synthesis of both natural products and medicinal chemistry targets.

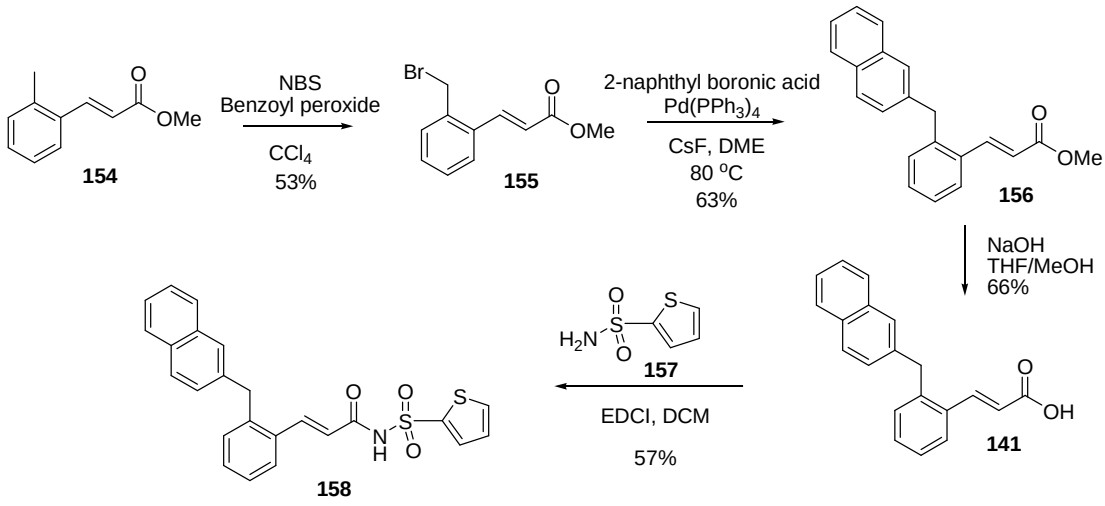


Figure 2.23 Merck synthesis of EP3 antagonist

Merck Frosst recently reported a series of EP3 prostanoid receptor antagonists which would be amenable to synthesis from benzyne. The literature procedure involves a five-step process from commercially available (E)-3-*o*-tolylacrylic acid, giving an overall yield of 12%, requiring the use of some toxic reagents as well as three chromatographic separations (Figure 2.23).[151] A successful three-step synthesis utilising the three component coupling gave a 61% overall yield (Figure 2.24). Reaction of naphthyl bromide with *tert*-butyl acrylate and benzyne proceeds efficiently, affording the acid **141** in an excellent 92% yield following treatment of the crude reaction mixture with TFA. Coupling to thiophene-2-sulfonamide **157**, using the procedure reported by Merck, then gave the EP3 antagonist **158** in an

overall yield of 61% for the three steps. Involving only one chromatographic separation, which is of the final product, the method would also be highly amenable to rapid library synthesis.

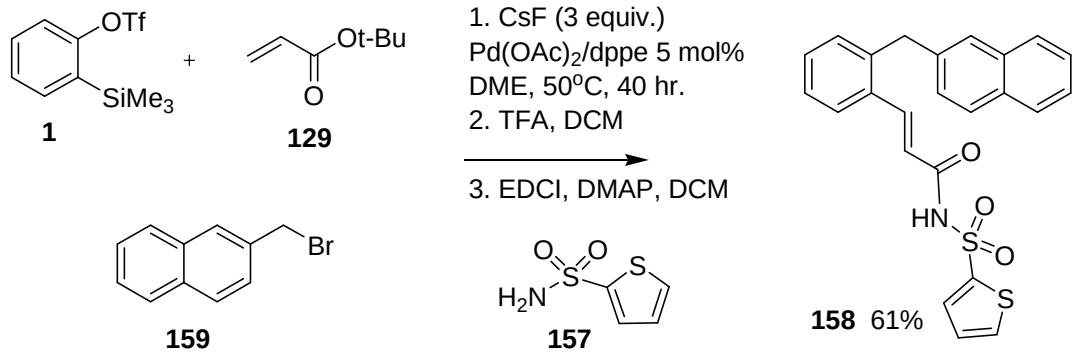


Figure 2.24 Synthesis of an EP3 receptor antagonist

The aryl-benzyl architecture is an important pharmacophore used in medicinal chemistry, with a number of compounds containing such a structural motif. The acrylate coupling partner also provides a handle for further elaboration of the products, with the possibility of forming amides using either ester, reduction of one ester group or of the double bond along with a range of other manipulations. Other compounds that could be synthesised in a straightforward manner using this technique are shown below (Figure 2.25); a chemokine receptor antagonist reported by Novartis[152] and Salvianolic acid D a natural product isolated from various members of the genus *Salvia*, which is used in many traditional Chinese medicines.[153]

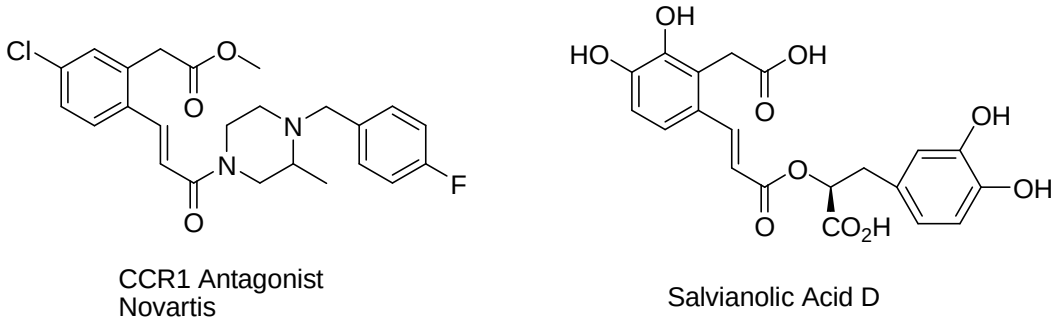


Figure 2.25 Other targets that could be synthesised using three component Heck coupling

2.8 Incorporating chirality

With reaction conditions in hand for the production of some interesting molecular architectures it was thought that a useful extension to this chemistry would be in the generation of compounds containing a stereocentre (Figure 2.26). It was envisioned that, were the reactions successful, a chiral phosphine ligand could then be employed in order to generate single enantiomers or enantiomerically enriched products.[154]

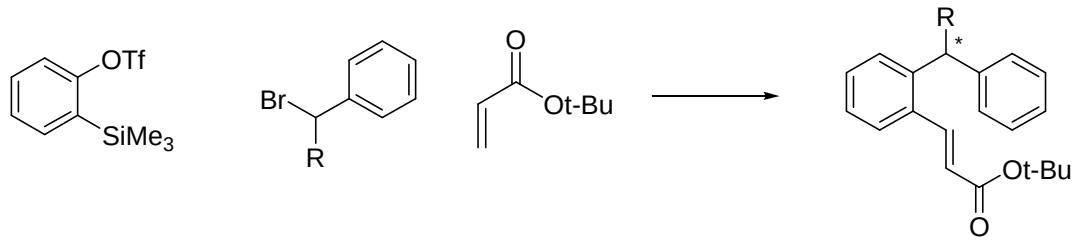


Figure 2.26 Example of three component coupling generating a new stereocentre

Unfortunately one major problem when addressing this consideration is that simple α-substituted benzyl bromides or acetates such as ethyl-2-bromopropanoate or 2-bromoethylbenzene contain a β-hydrogen so have the possibility of undergoing elimination immediately after oxidative addition, forming ethyl acrylate and styrene respectively (Figure 2.27).

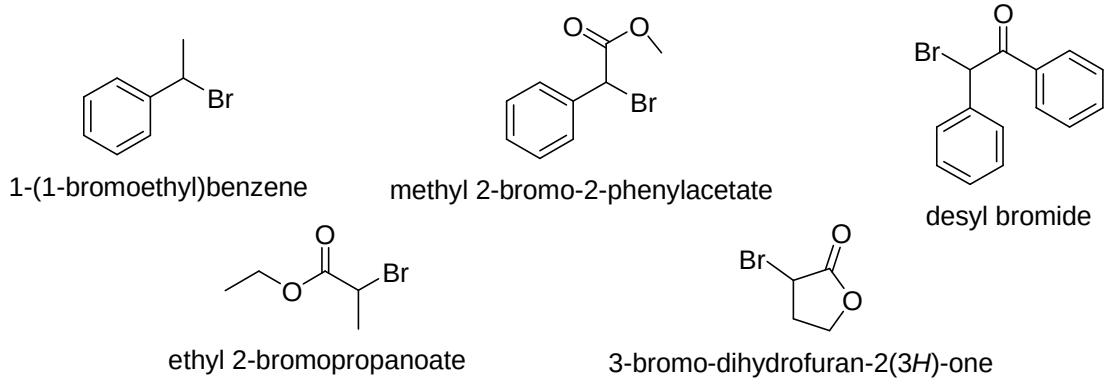


Figure 2.27 α-substituted benzyl bromides and bromoacetates

The first description of catalytic asymmetric cross-couplings of such electrophiles has been recently reported by Fu, nickel being utilised as the catalyst of choice in this case (Figure 2.28). Fu was able to successfully couple both α-bromo amides and secondary benzylic halides with organozinc reagents, in a nickel catalysed Negishi type reaction, a nitrogen based Pybox ligand conferring enantionselectivity.[154, 155] Mechanistically, Fu proposes the formation of a benzylic radical which then combines with nickel, as opposed to a more traditional oxidative addition. Indeed, these compounds have been seldom reported as substrates for palladium catalysed cross-coupling reactions.[156, 157] Nevertheless, as this would provide an interesting reaction and offer the opportunity to incorporate chirality it was considered to be a problem worth addressing.

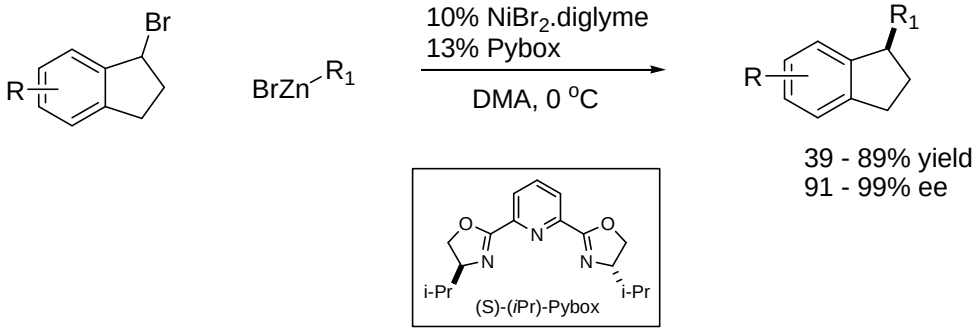


Figure 2.28 Nickel catalysed asymmetric cross coupling of secondary benzylic halides

One halide that would not suffer from the potential problem of β-hydride elimination is methyl α-bromophenylacetate (Figure 2.27). Three component coupling of this substrate using conditions as per bromoacetates or benzyl bromides did not yield any of the desired product. A complex mixture was obtained, which contained amongst other things, triphenylene and dihydrophenanthrene. There are two possible problems with this substrate. Firstly, although the α-position is doubly activated, the steric bulk around the centre may make oxidative addition considerably slower than the unsubstituted compounds. Also, literature reports of attempts to utilise the substrate in Suzuki reactions found that the homo-coupling of the boronic acid was the sole outcome, with no trace of their intended product.[158, 159] The authors attributed this to the palladium species formed favouring the Pd-oxygen (η^1) enolate

(Figure 2.29), transmetallation of the boronic acid to the palladium species then cleaving the palladium-oxygen bond. Utilising the unsubstituted α-bromo ethylacetate cross-coupling could be achieved in yields of 70%, however increasing the steric bulk (desyl bromide) further enhanced the yield of homo-coupling, suggesting that steric rather than electronic factors are the issue. The authors have gone on to extend the utility of this homocoupling to the Negishi reaction, zinc transmetallation cleaving the palladium-oxygen bond.[159]

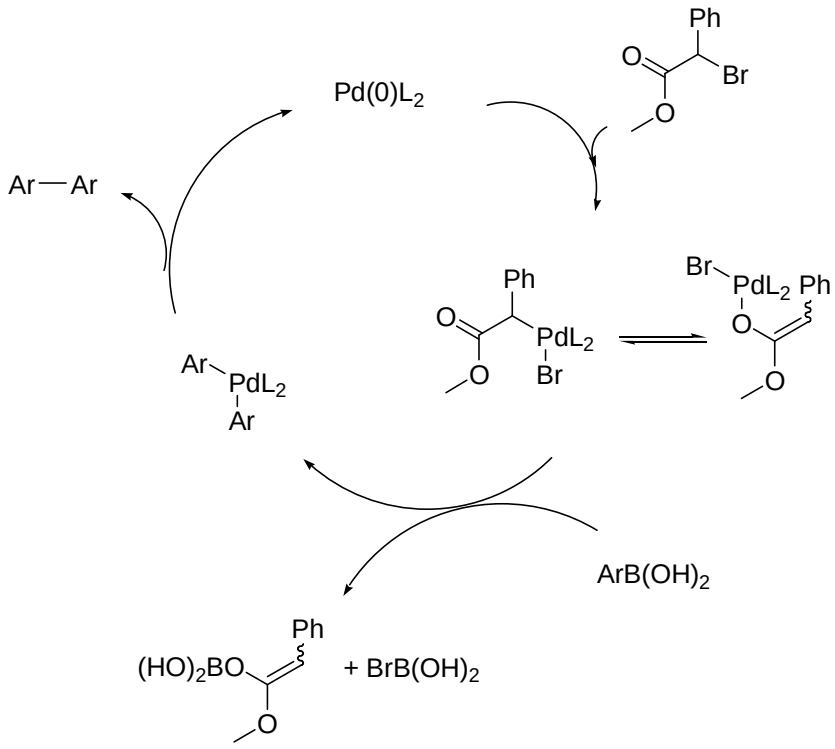
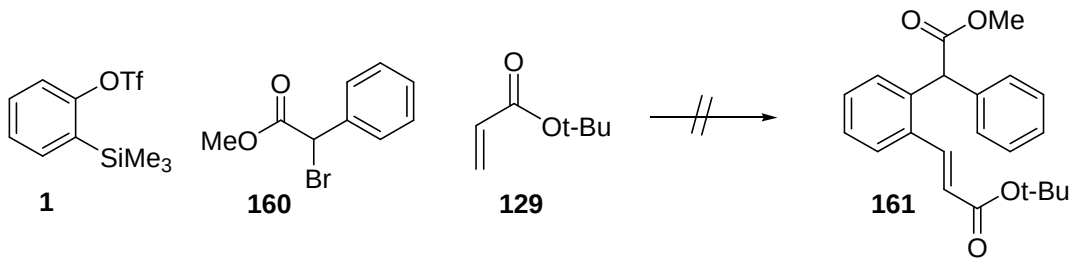


Figure 2.29 Proposed mechanism of homocoupling promoted by substituted α-bromoketones

In order to generate a successful cross-coupling reaction using these compounds the issue of palladium-oxygen (η^1) *vs* either palladium-π-allyl (η^3) or palladium-carbon (η^1) coordination will need to be addressed so as to avoid deleterious side reactions. By changing the palladium ligands and hence both the steric and electronic properties of the palladium centre it should be possible to alter the equilibrium state in favour of carbon over oxygen coordination. Thus a screen of various reaction conditions was carried out using both standard mono- and bidentate phosphine ligands along with a selection of chiral phosphine ligands (Table 2.9, Figure 2.30).[160] A similar outcome may be achieved by changing the counter-ion on palladium from

a strongly coordinating halide to acetate or carbonate which coordinate more weakly. Salt additives silver carbonate and thallium acetate were also used to promote the coupling reaction.

Table 2.9 Screen of conditions for three component coupling using methyl 2-bromo-2-phenylacetate



Entry	Pd Source	Ligand	Solvent	Time	Temp.	Additive
1	$Pd(OAc)_2$	P(*o*-tol)$_3$	MeCN	4 h	45 °C	
2	$Pd(OAc)_2$	P(*t*-Bu)$_3$.HBF_4	MeCN	4 h	45 °C	
3[a]	$Pd(OAc)_2$	J002	MeCN	4 h	45 °C	
4[a]	$Pd(OAc)_2$	J005	MeCN	4 h	45 °C	
5	$Pd(OAc)_2$	P(*o*-tol)$_3$	MeCN/Tol (1:2)	o/n	80 °C	
6	$Pd(OAc)_2$	P(*t*-Bu)$_3$.HBF_4	MeCN/Tol (1:2)	o/n	80 °C	
7	$Pd(OAc)_2$	dppe	MeCN/Tol (1:2)	o/n	80 °C	
8	Pd(dppf).Cl_2		MeCN/Tol (1:2)	o/n	80 °C	
9	$Pd(OAc)_2$	R-Solphos	DME	o/n	50 °C	
10	Pd(dppf).Cl_2		DME	o/n	50 °C	
11	$Pd(OAc)_2$	dppe	DME	o/n	50 °C	Ag_2CO_3
12	$Pd(OAc)_2$	dppe	DME	o/n	50 °C	$Tl(OAc)_2$
13	Pd(dppf).Cl_2		DME	o/n	50 °C	Ag_2CO_3
14	Pd(dppf).Cl_2		DME	o/n	50 °C	$Tl(OAc)_2$
15	PEPPSI		DME	o/n	50 °C	

Reactions carried out using 5 mol% catalyst/ligand, in 1 mL of solvent with a **1:160:129** ratio of 1:1.5:1.2. [a] Ratio of **1:160:129** was 2:1.5:1

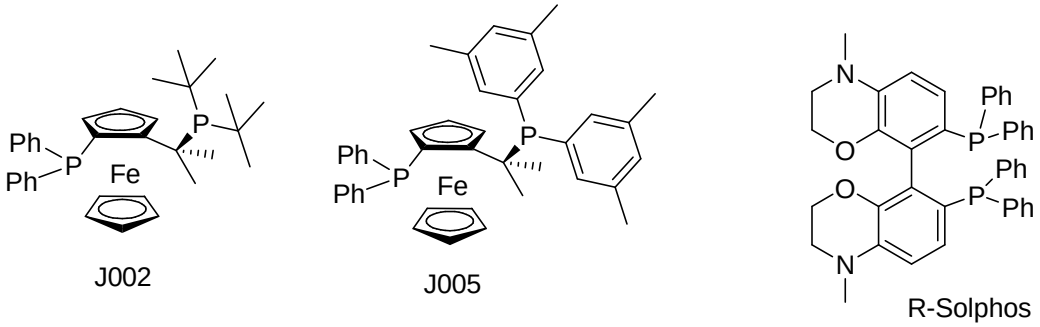


Figure 2.30 Chiral ligands used

No evidence of three component coupling was observed under a range of conditions, a suitable peak for the *tert*-butyl group being absent by NMR of the crude reaction. Under most conditions, with the exception of MeCN/Toluene at 80 °C, the benzyne precursor was fully consumed, triphenylene being the only obvious benzyne containing product. Methyl 2-bromo-2-phenylacetate **160** was also absent from the NMR of the reaction, appearing to have been proto-debrominated to yield methyl 2-phenylacetate. As none of the reactions showed evidence of yielding the desired product full characterisation of the products was not undertaken.

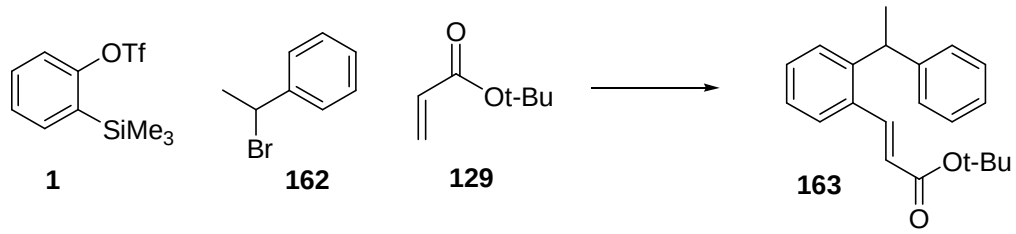


Figure 2.31 Three component coupling using 2-bromoethylbenzene

Although 2-bromoethylbenzene **162** does contain a β-hydrogen, if a suitably fast reaction with benzyne could be achieved, the deleterious styrene formation would be suppressed (Figure 2.31). Reactions carried out with a range of palladium/ligand systems in both DME and MeCN at 50 °C showed only unreacted 2-bromoethylbenzene and triphenylene. A range of other solvents or temperatures were not used for this substrate. Observation by NMR of unreacted 2-bromoethylbenzene suggested that in this case oxidative addition of the substrate was slow, as opposed to being consumed by β-hydride elimination.

2.9 Substituted aryne precursors

Along with the results reported above (Figure 2.19) a range of other substituted benzyne precursors were used in the reaction, with little success (Figure 2.32). There appeared to be no single distinctive issue as to the failings of the reactions, with neither traces of product nor multi-benzyne containing compounds such as the triphenylenes being isolated. A number of causative factors could be postulated; the precursors could be more sensitive to moisture. Stabilisation of the anion formed from loss of the TMS group could lead to protonation before benzyne is formed. The hypervalent silicon species could also be stabilised by substituents on the ring, making a Hiyama type reaction more likely and preventing the formation of the aryne. Changing the electronics and sterics of the aryne will also affect both the rate of formation and the rate of addition to the palladium species. Indeed this may prove to be an inherent problem with palladium/aryne couplings – where the rates of different reactions are finely balanced it may prove difficult to achieve good yields using the same palladium catalyst and reaction conditions with different arynes.

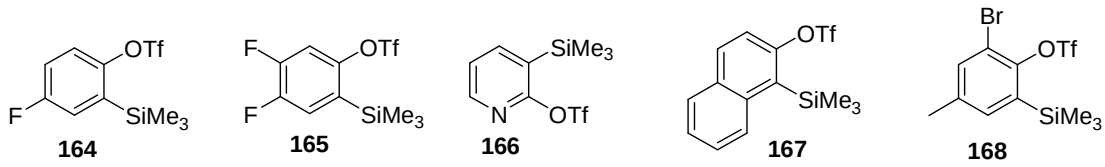


Figure 2.32 Alternative arynes used unsuccessfully in 3CC

Of the arynes that yielded a successful 3CC reaction, both contained electron donating methyl groups. Electron withdrawing groups, mono- or di-fluorobenzyne precursors, were not well tolerated and did not yield successful reactions, suggesting that electronic factors play an important role. As a 3,6-disubstituted aryne gives only a small drop in yield it appears steric factors may be less of an issue.

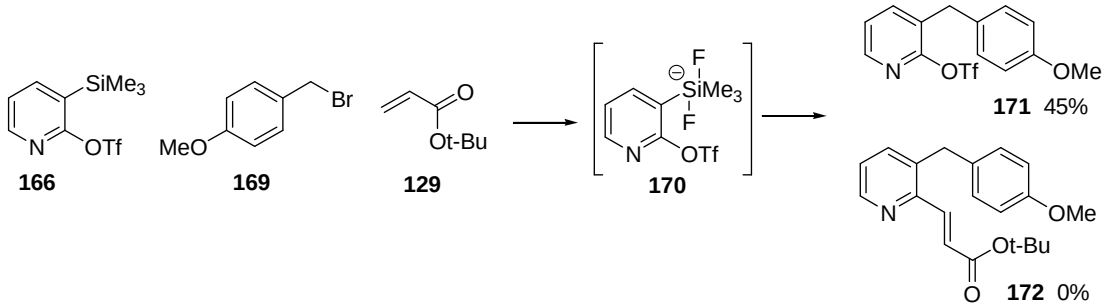


Figure 2.33 A Hiyama reaction occurs when 2,3-pyridyne precursor is used

Although many of the reactions did not yield any isolable, identifiable products, reaction of the pyridyne precursor (**166**) with benzyl bromide and acrylate yielded the Hiyama product, 3-benzylpyridin-2-yl trifluoromethanesulfonate **171**, in a yield of 45% (Figure 2.33). This suggests the hypervalent fluoride species **170** is stabilised by the pyridine nitrogen, allowing the cross-coupling to take place. In this case, it may be possible to alter the precursor by changing the positions of the triflate and TMS groups to induce more rapid formation of the aryne. It may also be beneficial to utilise the 3,4-pyridyne instead of 2,3-pyridyne; in reports on the reaction of these two species, generated from the respective silyl triflates, it was found that the former gave a 3-fold increase in yield of the Diels-Alder product.[37, 39] Historically 3,4-pyridyne has received more attention from the synthetic community in terms of generation methods and synthetic potential, 2,3-pyridyne having been branded a 'hetaryne problem child'.[161]

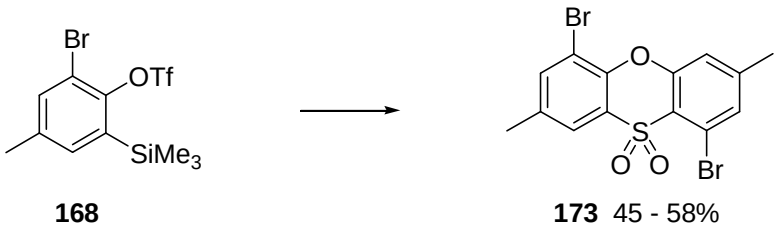


Figure 2.34 Unexpected product from coupling reaction using 2-bromo-4-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate

Table 2.10 Phenoxathiiin **173** was generated under various reaction conditions

Entry	Catalyst	Solvent	Time (h)	Yield (173) %
1[a]	$Pd(OAc)_2$/dppe	DME	24	58
2	$Pd(OAc)_2/P(o\text{tol})_3$	MeCN	4	53
3	none	MeCN	4	51

Reactions were carried out on a 0.3 mmol scale, with 3 equiv. CsF and 5 mol% catalyst in 1 mL solvent at 50 ºC. [a]In the presence of benzyl bromide and *t*-butyl acrylate

Reactions involving 2-bromo-4-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (**168**) also yielded an unexpected product under three-component coupling conditions (Figure 2.34). 1,6-Dibromo-3,8-dimethyl-phenoxathiin 10,10-dioxide (**173**) was isolated in a yield of 58% from the reaction with bromomethylacetate and *tert*-butyl acrylate, the product being conclusively identified by X-ray crystallography after extensive NMR studies (Figure 2.35). Whether the mechanism of this unusual reaction involves aryne formation is unclear. A similar 53% yield could be achieved using a different catalyst system in acetonitrile after only 4 hours, more rapid generation of aryne being expected in this solvent. In the absence of palladium **173** was again isolated, in a 51% yield, thus this is probably not a palladium mediated process (Table 2.10).

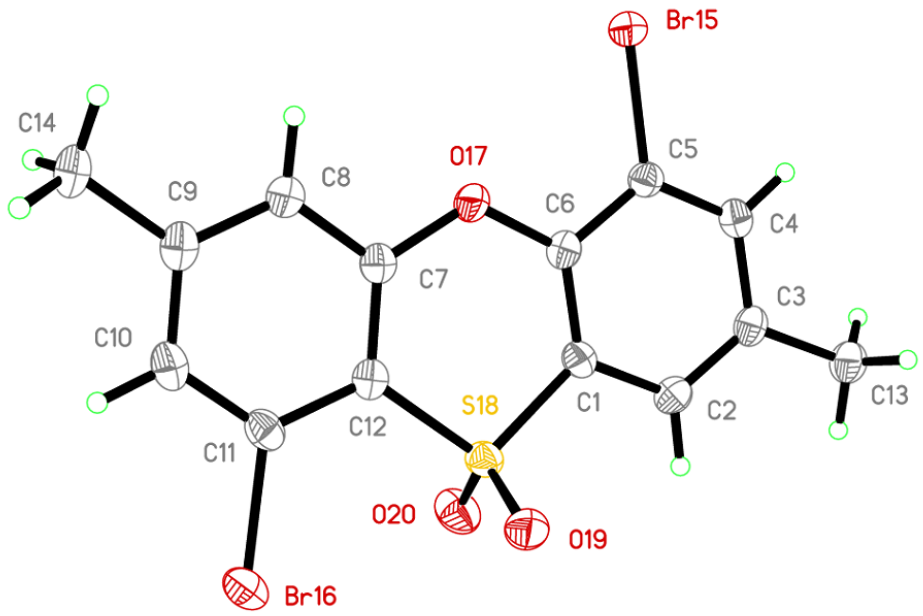


Figure 2.35 X-ray crystal structure of 1,6-dibromo-3,8-dimethyl-phenoxathiin 10,10-dioxide **173**

A possible mechanism for the formation of such a product is shown below (Figure 2.36). If the anion formed (**174**) is stable, or the triflate less prone to eliminate, an anionic thia-Fries rearrangement could occur.[45, 162] The phenoxide anion then formed (**175**) could react with benzyne **176**, occurring at the less sterically hindered end of the triple bond. Attack of the phenyl anion at the sulfonyl group with elimination of the trifluoromethyl group then would yield the identified product. Regiochemical selectivity can be explained by both steric and electronic factors, the anion adjacent to the bromine being partially stabilised by the electron withdrawing halide, as well as keeping the sterically bulky bromine atoms apart. It is harder to explain why the aryne is generated in some cases and the thia-Fries rearrangement occurs in others, thus an alternative pathway may be in operation. To help establish if this mechanism is in operation, unsubstituted benzyne precursor **1** was reacted with **168** in both the absence and presence of a palladium catalyst (Figure 2.37). It was expected that a mixture of tetra-substituted (**173**) and disubstituted phenoxathiins would be formed if a species such as **175** is reacting with an aryne. However, **173** was the only phenoxathiin isolated.

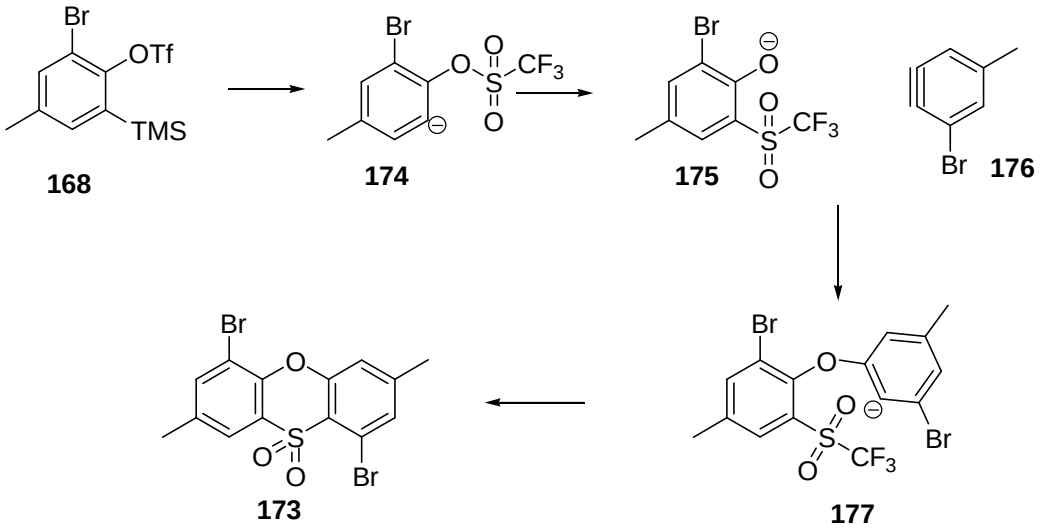


Figure 2.36 Proposed mechanism for formation of 1,6-dibromo-3,8-dimethyl-phenoxathiin 10,10-dioxide **173**

An alternative way to validate the mechanism would be to react benzyne with an *ortho*-substituted 2-(trifluoromethylsulfonyl)phenol or phenoxide. If similar compounds could be generated, this would certainly lend credence to this mechanism. However failure to produce unsymmetrical compounds through combination of **168** with the unsubstituted benzyne precursor **1** suggests that no aryne is involved (Figure 2.37).

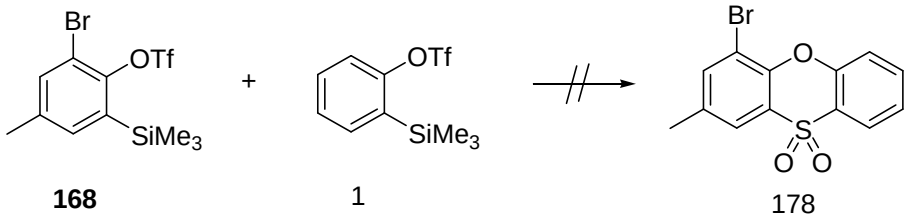


Figure 2.37 Reaction between substituted and unsubstituted benzyne precursors **168** and **1** did not yield an unsymmetrical phenoxathiin.

3 Aryl Halides in the Heck Reaction

Moving on from the successful Heck reaction with benzyl bromides and α-bromo acetates it was felt that the application of aryl halides in this chemistry would further improve the structural diversity and application of the reaction. As has been previously mentioned, at the outset of these investigations few examples of the use of aryl halides in palladium-catalysed benzyne couplings had been reported. Most of these examples involve either two components or a cyclisation step so development of this chemistry would be an important advance.

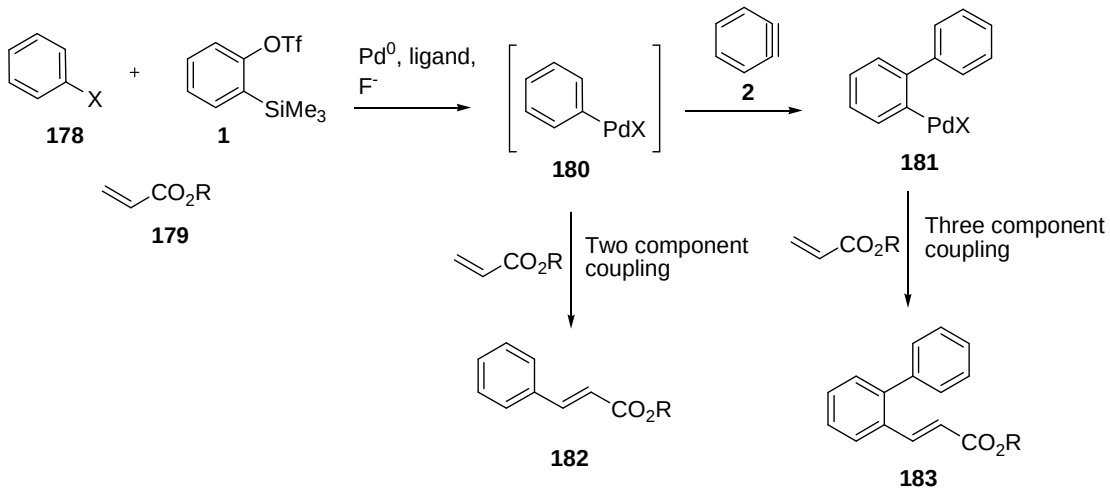


Figure 3.1 Challenge of developing a three component coupling with aryl halides

One of the major challenges in such a system concerns the *o*-arylpalladium (II) complex **180** generated by oxidative addition of the aryl halide, being far more reactive than analogous benzyl or allylpalladium (II) species. Ensuring reaction of this palladium species with an aryne, another reactive intermediate, would seem to be a demanding requirement. In comparison to the previous reactions where two component coupling was unlikely to be a significant issue, the Heck reaction of aryl halides with acrylates is well developed, and thus 2CC is likely to be a difficult challenge to overcome. Also, the intermediate palladium species after oxidative addition of the aryl halide (**180)** and carbopalladation of benzyne (**181**) will be

similar, both containing an aryl-palladium bond, thus selectivity for the more sterically hindered of the two systems may prove a complex problem (Figure 3.1).

3.1 Initial Studies

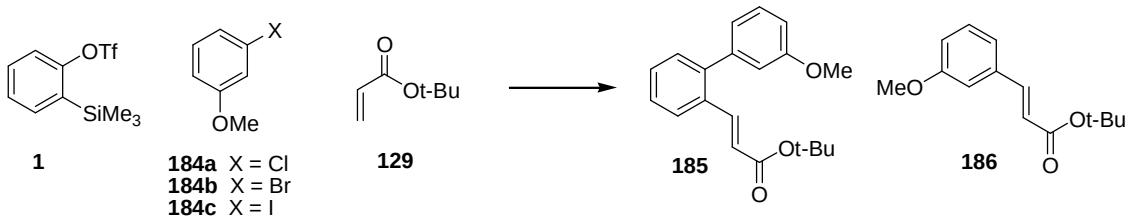


Figure 3.2 3CC with aryl halides

Initial studies into the use of aryl halides as coupling partners in the Heck reaction yielded poor results. Using the conditions developed for benzyl bromides, namely a $Pd(OAc)_2$/dppe catalyst system in DME, no product was formed with 3-iodo-, 3-bromo-, or 3-chloroanisole (Figure 3.2). In all three cases the major product was triphenylene, with (E)-*tert*-butyl 3-(3-methoxyphenyl)acrylate (**186**) and benzyne-benzyne-alkene coupling products (**131)** also detected. A simple change of solvent from DME to acetonitrile showed promising results, the first traces of three-component coupling product (**185**) being observed with 3-iodoanisole. Bromo- and chloro- derivatives again gave no 3CC. A yield of ~6% was achieved, although isolated as a mixture with 2CC product, however doubling the amount of benzyne used increased the yield to 16%. Following this a screen of catalyst systems was carried out, showing monodentate phosphine ligands to be superior, the best results being initially achieved with *o*-tolyl, 2-furyl and *t*-butyl phosphines (Table 3.1).

Table 3.1 Initial Screen of phosphine ligands

Entry	Pd Source	Ligand	3CC (185) (%)	2CC (186) (%)	Triphenylene (%)
1	$Pd(PPh_3)_4$		6	60	33
2	$Pd(dppf).Cl_2$		10	45	43
3	$Pd(OAc)_2$	dppe	6	74	23
4	$Pd(OAc)_2$	P(*o*-tol)$_3$	23	24	58
5	$Pd(OAc)_2$	P(fur)$_3$	21	36	5
6	$Pd(OAc)_2$	dppp	0	78	65
7	$Pd(OAc)_2$	DPEPhos	17	48	31
8	$Pd_2(dba)_3$	dppe	7	47	58
9	$Pd_2(dba)_3$	P(fur)$_3$	11	22	n.d.
10	$Pd(OAc)_2$	P(*t*Bu)$_3$.HBF_4	18	35	8
11	$Pd(OAc)_2$	P(Cy)$_3$	8	25	52
12	$Pd(OAc)_2$	TDMPP	16	45	22

Reactions were carried out using a 1:1:1 ratio of **1:184c:129** with 5% Pd/ligand and CsF 3equiv. in MeCN at 50 °C for 48 hrs.

Yields in these cases were determined by NMR of the isolated mixture, as the 2CC and 3CC products are inseparable by silica chromatography, although can be easily purified by HPLC or SFC. Using these techniques it was shown that the ratio determined by NMR was representative of the sample. Repeating the reactions with 4-trifluoromethyliodobenzene, 4-methyliodobenzene or iodobenzene also gave evidence of 3CC, however the two products were harder to distinguish by NMR (Figure 3.3). As it was important to have a system that gave clear results in order to easily monitor and assess the reactions, 3-iodoanisole was chosen for further optimisation studies. Due to its electronic properties, however, it may not prove to be optimum for this reaction.

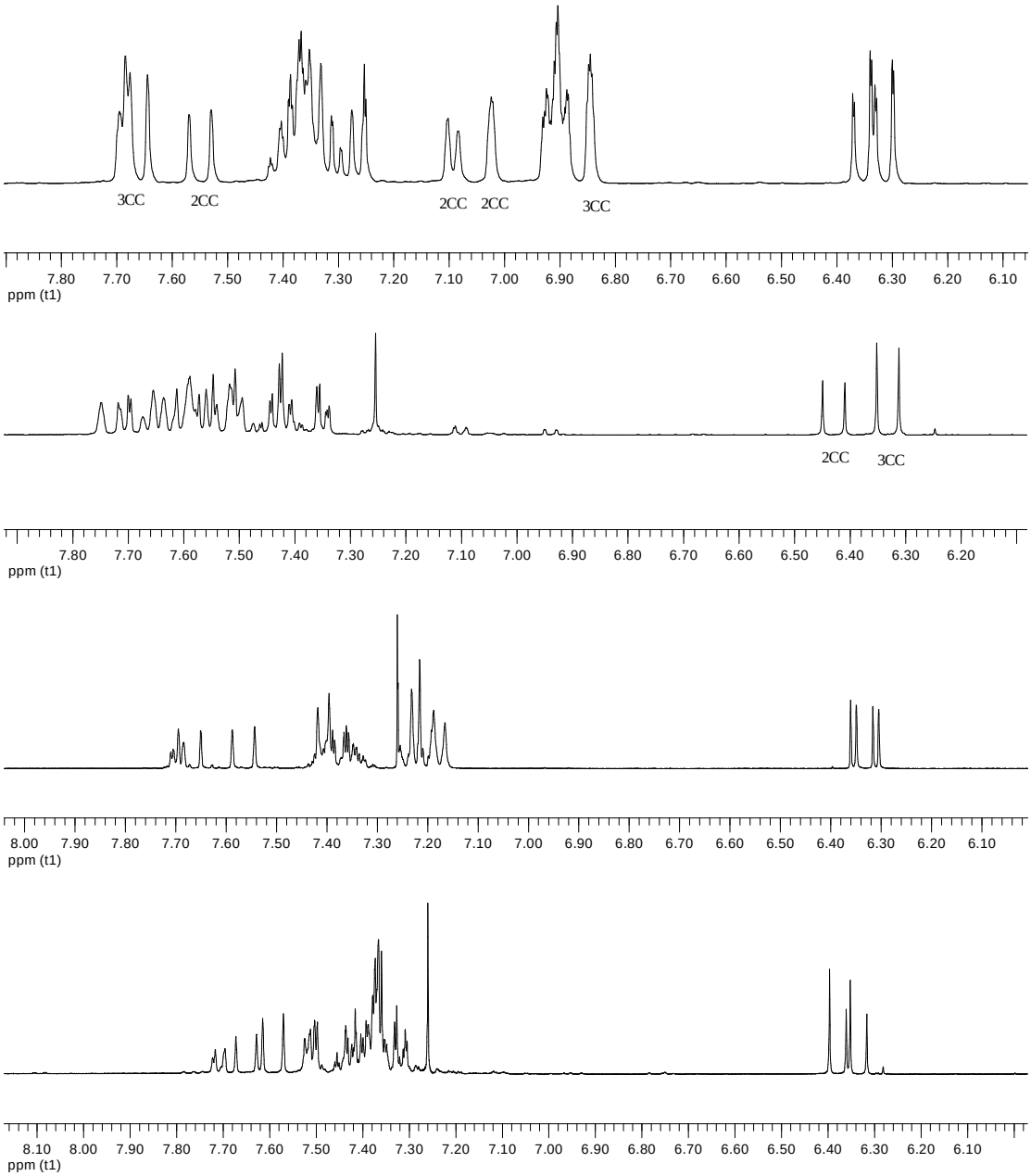


Figure 3.3 NMR showing distinctions between 2CC and 3CC products (from top 3-OMe, 4-CF_3, 4-Me and iodobenzene)

Similar to the allyl-type systems there are mechanistically two potential ways in which the reaction could proceed, both of which can give triphenylene and 2CC by-products. Firstly, it could be considered that benzyne is required to react with palladium as the first step in the catalytic cycle, giving an η^2-palladium complex. Alternatively the oxidative addition of the aryl halide could be the initial step. In the latter case two reactive intermediates are reacting thus implying the former is more

plausible. In terms of the large quantities of both 2CC and triphenylene are being generated, either pathway is reasonable. If the reaction of benzyne with palladium is the fast step, this then causing oxidative addition to be slow or preventing it entirely, then large amounts of triphenylene will be generated at the beginning of the reaction, the Heck reaction then occurring after all the benzyne has been consumed. The faster step could also be the Heck reaction, aryl-palladium species reacting quicker with the more abundant acrylate after oxidative addition, leaving benzyne to co-trimerise after other starting materials have been consumed.

The reaction could also be considered in terms of the palladium species present in the reaction and the order in which these must be formed for a successful outcome. For example if the first step in the catalytic cycle is the oxidative addition of aryl halide to palladium this must occur faster than the coordination of benzyne. However the second step in the reaction, addition of benzyne to this species must be more rapid than the acrylate otherwise 2CC will be formed. As the acrylate is more abundant in solution this would be the kinetically favoured outcome. The second potential mechanistic pathway would begin with coordination of benzyne to palladium to give an η^2-palladium complex, followed by reaction of this species with aryl halide. This second step must proceed at a higher rate than reaction with a second benzyne molecule to prevent the formation of multi-benzyne containing products. Reaction of the biaryl-palladium species with acrylate would then terminate the sequence, and must proceed more rapidly again than reaction with benzyne, otherwise substituted triphenylenes will be the major product. If this latter pathway is followed it could be postulated that aryl iodides are likely to react too quickly with palladium, preventing formation of the η^2-palladium complex, therefore the use of aryl bromides or chlorides should prove to be a more successful strategy. If the former mechanism is in place more rapid generation of benzyne and use of more nucleophilic, electron-rich palladium complexes should provide the most promising results.

3.2 Optimisation Studies

Having considered some of the potential pathways which could be occurring, initial studies concentrated on the examining the reaction timeframe (Table 3.2). Utilising the preferred catalyst from the initial reactions a pattern appeared to be emerging where the ratio of 3CC vs 2CC was higher at the outset of the reaction, thus indicating benzyne was being quickly consumed, mainly forming triphenylene. Triphenylene formation was found to occur even at room temperature, with no Heck reaction being observed. It should also be noted that even after extended reaction periods less than 50% of the aryl iodide has undergone a successful Heck reaction, suggesting that the catalyst system may be poor for this substrate.

Table 3.2 Investigation of 3CC over varying time courses

Entry	Time (h)	3CC (185) (%)	2CC (186) (%)
1	1	23	10
2	2	34	15
3	4	27	31
4	48	23	24

Reactions were carried out using a 1:1:1 ratio of **1:184c:129** with 5% $Pd(OAc)_2/P(o\text{-tol})_3$ and CsF 3equiv in MeCN at 50 °C.

In order to increase the amount of benzyne available for three-component coupling and minimise losses in yield to triphenylene, a range of stoichiometries were investigated (Table 3.3). An excess of benzyne combined with an excess of one of the other two reagents gave a two-fold increase in yield, giving improvements over increasing the equivalency of benzyne alone. Further increasing the number of equivalents of the aryl iodide used was found to be detrimental to the reaction, formation of substituted triphenylenes being observed in those cases.

Table 3.3 Examination of reagent stoichiometries

Entry	Ratio 1:184c:129	3CC (185) (%)	2CC (186) (%)
1	1:1:1	23	10
2	2:1:1	35	19
3	2:1.5:1	43	16
4	2:1:1.5	42	14

Reactions were carried out with 5 mol% $Pd(OAc)_2$/P(*o*-tol)$_3$ and CsF in MeCN at 50 °C for 1 hour.

An alternate way of ensuring benzyne is available throughout the reaction would be to add the precursor slowly. A large number of reactions were performed where benzyne was added either portion-wise or via a syringe pump, with addition of either benzyne or both benzyne and acrylate being examined (Table 3.4). Results using a syringe pump were poorer than may have been expected, probably due to the difficulty in adding small quantities, and the necessity to add extra solvent to increase the addition volume. Although some of these procedures gave good yields it was felt that the simplicity and time savings achieved from two additions of benzyne would be the most promising conditions to take forward for further optimisation studies.

Table 3.4 Examples of slow addition experiments

Entry	What was added	Addition method	No. of additions	Addition Interval (min)	Total addition time (min)	3CC (185) (%)	2CC (186) (%)
1	Benzyne and acrylate in MeCN	Syringe	25	2	50	42	14
2	Benzyne	Syringe	10	5	45	55	36
3	Benzyne	Syringe	4	30	120	54	33
4[a]	Benzyne	Syringe	2	60	60	62	30
5	Benzyne and acrylate in MeCN	Syringe Pump			120	43	10

Reactions were carried out with 5% $Pd(OAc)_2$/P(*o*-tol)$_3$ and CsF 6 equiv. in MeCN at 50 °C. [a] 45 °C.

As selectivity for 3CC *vs* 2CC was slowly improving a small screen of alternative reaction temperatures was also carried out, showing that a 5 ºC drop in temperature increased both yield and selectivity of the reaction (Table 3.5). Dropping the temperature further was detrimental, Heck coupling presumably occurring too slowly. Studies were also performed using microwave heating over various time periods and temperatures however only 2CC was observed, with the benzyne precursor recovered unchanged.

Table 3.5 Screen of reaction temperatures

Entry	Temperature (ºC)	3CC (185) (%)	2CC (186) (%)
1	40	37	15
2	45	62	30
3	50	55	36
4	100 (MW)	0	

Reactions were carried out with 5% $Pd(OAc)_2$/P(*o*-tol)$_3$ and CsF 6 equiv. in MeCN

As changes in reagent stoichiometry, addition rate, reaction time and temperature had given enhanced yields, a second screen of catalyst/ligand systems was undertaken (Table 3.6). Despite screening a wide range of monodentate phosphines, none was found to be superior to P(*o*-tol)$_3$, although the bulky ligand P(*t*-Bu)$_3$.HBF$_4$ (Entry 9, Table 3.6) was found to give a similar selectivity with only slightly attenuated yield. Bidentate ligands were again found to be poor, dppe for example yielding no Heck product (Entry 3, Table 3.6). A range of other palladium sources were also considered, however neither alternative Pd(II) nor Pd(0) sources gave an improvement over Pd(OAc)$_2$. No reaction occurred using NHC ligand PEPPSI nor Pd(succinimide) as catalysts (Entries 5, 13 and 14, Table 3.6), and a nickel catalyst was also not successful (Entry 19, Table 3.6). Given the effectiveness of P(*o*-tol)$_3$ amongst ligands surveyed for the reaction, and the failure of related monodentate ligands such as PPh$_3$ or P(2-fur)$_3$, it was considered that *in situ* formation of the Herrmann-Beller palladacycle could be responsible for the efficiency of this catalyst system.[163] Indeed, the preformed palladacycle was effective in the 3CC however giving a slightly ameliorated yield in comparison to the Pd(OAc)$_2$/P(*o*-tol)$_3$ system (Entry 18, Table 3.6).

Table 3.6 Second screen of palladium/ligand systems using optimized conditions

Entry	Pd Source	Ligand	3CC (%)	2CC (%)
1	$Pd(PPh_3)_4$		No reaction	
2	$Pd(dppf).Cl_2$		18	18
3	$Pd(OAc)_2$	dppe	No reaction	
4	$Pd(OAc)_2$	P(*o*-tol)$_3$	62	30
5	PEPPSI		No reaction	
6	$Pd(OAc)_2$	TDMPP	45	23
7	$Pd(OAc)_2$	DPEPhos	42	28
8	$Pd(OAc)_2$	PBiPh(*t*-Bu)$_2$	31	18
9	$Pd(OAc)_2$	P(*t*-Bu)$_3$.HBF_4	48	29
10	$Pd(OAc)_2$	PPh_3	9	18
11	$Pd_2(dba)_3$	P(*o*-tol)$_3$	43	18
12	$Pd_2(dba)_3$	P(*t*-Bu)$_3$.HBF_4	16	28
13	Pd(succinimide)		No reaction	
14	Pd(succinimide)	P(*o*-tol)$_3$	No reaction	
15	$PdCl_2$	P(*o*-tol)$_3$	No reaction	
16	$PdCl_2(PhCN)_2$	P(*o*-tol)$_3$	No reaction	
17	$Pd(OAc)_2$		No reaction	
18	Herrmann-Beller Palladacycle		43	26
19	$Ni(dppe)Cl_2$		No reaction	

Reactions were carried out with 5% Pd/ 10% ligand and CsF (6 equiv.) in MeCN at 45 ºC for 4 hours.

The ratio of palladium to ligand was also thought to play a potential role in the reaction, as an increase in this ratio should ensure that the palladium species in solution are at a low oxidation state and that palladium does not precipitate out of the reaction. Pd(II) can catalyse formation of triphenylene whereas a successful Heck reaction is likely to require Pd(0). It was found that a 2:1 ratio of ligand to palladium was optimal for the reaction when using P(*o*-tol)$_3$, as a higher ratio leads to increased 2CC whilst a lower ratio gives decreased yield (Table 3.7). A similar pattern was seen using P(*t*-Bu)$_3$.HBF_4, a small increase of 2CC being observed, although ligand ratio had a more subdued effect in this system.

Table 3.7 Variation of ligand to palladium ratio

Entry	Pd source	Ligand	Ligand/Pd ratio	3CC (%)	2CC (%)
1	$Pd(OAc)_2$	P(*o*-tol)$_3$	1:1	42	19
2	$Pd(OAc)_2$	P(*o*-tol)$_3$	2:1	62	30
3	$Pd(OAc)_2$	P(*o*-tol)$_3$	4:1	51	47
4	$Pd(OAc)_2$	P(*t*-Bu)$_3$.HBF_4	1:1	50	20
5	$Pd(OAc)_2$	P(*t*-Bu)$_3$.HBF_4	2:1	48	27
6	$Pd(OAc)_2$	P(*t*-Bu)$_3$.HBF_4	4:1	46	29

Reactions were carried out with 5% Pd and CsF (6 equiv.) in MeCN at 45 ºC for 4 hours.

Different salts were also added to the reaction in an attempt to modify the counterion on palladium and hence affect the reactivity. Ag_2CO_3, $Tl(OAc)_2$ and LiCl were all well tolerated, not adversely affecting the yield nor ratio of products, however giving no improvement in either. Copper salts, CuI and $CuCl_2$ surprisingly suppressed benzyne generation. It is not clear how this is occurring, whether they perhaps decrease the solubility of the fluoride ions or if there is a more subtle change to the system.

Table 3.8 Screen of reaction solvent

Entry	Solvent(s)	Ratio	3CC (%)	2CC(%)
1	MeCN		62	30
2	Acetone		32	42
3	THF		No reaction	
4	2-Butanone		27	55
5	DME		21	25
6	DME[a]		28	38
7	DCM		No reaction	
8	DCM/MeCN	10:1	Only 2CC	
9	DME/MeCN	4:1	39	39
10	DME/MeCN	9:1	35	53
11	DME/MeCN	99:1	23	29

Reactions were carried out with 5% Pd/ 10% P(*o*-tol) and CsF (6 equiv.) at 45 ºC for 4 hours. [a] 6 hours

Concurrent to optimisation of other parameters, a screen of solvents was carried out, as in the previous reaction systems, and work reported by other groups, this had proved an effective way to control the rate of benzyne generation. Solvents such as 2-butanone and acetone were chosen as they have a dielectric constant in the same region as acetonitrile so it was envisioned that they might offer a small change in generation rate, CsF being around 3-fold less soluble in DME than in MeCN.[164] No solvent offered superior results to reaction in acetonitrile (Table 3.8). Generation of benzyne did not occur using either THF or DCM under the reaction conditions, and a significant quantity of the precursor remained after reaction in DME. A longer reaction time in this solvent improved slightly on the result, however as the major product was 2CC this was not pursued. As can be seen from the results using mixed solvent systems, addition of acetonitrile does increase the rate of benzyne generation, even when used as only 10% of the mixture; however a solvent mix that yielded enhanced results was not discovered. Interestingly DME does give efficient coupling when 3-chloroiodobenzene is used, giving an equivalent yield to reaction in MeCN. The drawback, however, is that 2CC product is also isolated in a yield of 26%, compared to only trace quantities being observed in MeCN.

3.3 Results

With conditions in hand for a reasonably successful three component coupling some initial forays were made with other available aryl iodides to examine the scope and limitations of the reaction. In fact, it proved to be far more successful when applied to other substrates, again illustrating that perhaps an alternative substrate would have made for a faster optimisation.

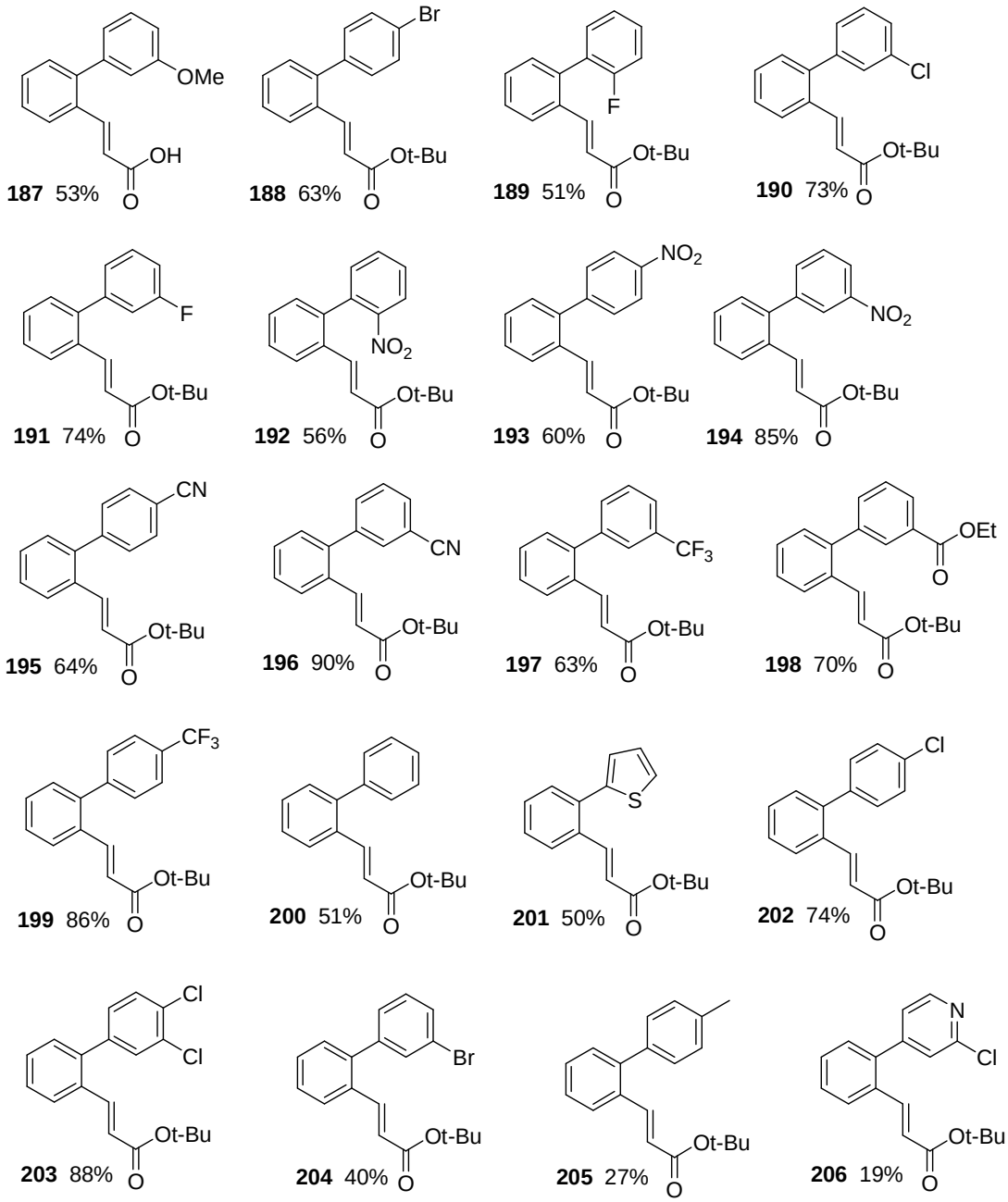


Figure 3.4 A range of aryl halides can be successfully used for 3CC

Diverse aryl iodides could be utilised in the reaction, with electron poor substrates proving to be the most efficient, giving high yields and little 2CC (Figure 3.4). A wide range of reactive functional groups such as cyano- and nitro- were well tolerated, as were halogen substituted aryl iodides, which gave excellent yields with no evidence of any second Heck coupling or other interference from the halide. Similar to 3-iodoanisole, electron rich precursors gave mixtures of 3CC and 2CC

products which were difficult to separate. The yields reported here for the unsubstituted phenyl **200** (51% pure *vs* 60% total), *para*-methyl **205** (27% *vs* 44%) and *meta*-bromo **204** (40% *vs* 62%) as well as *meta*-trifluoromethyl **197** (63% *vs* 89%) are all significantly lowered by some 3CC being lost as mixtures with 2CC, and other electron rich substrates such as 3-iodotoluene produced inseparable mixtures (Figure 3.5). 2-Iodoanisole did not yield any of the desired product, the aryl halide failing to react even at extended reaction times or higher temperatures. Looking at a range of other ligands with this substrate did yield some 2CC product but only traces of 3CC were observed. Heteroaromatic iodides could also be used, 2-iodothiophene giving 50% yield (**201)** and 2-chloro-4-iodopyridine yielding 18% (**206)**. The product from the latter reaction was isolated by HPLC as reactions with this and the other iodopyridine regioisomers yielded black tarry products which were inseparable and streaked upon silica chromatography (Figure 3.5). This result does illustrate that couplings of arynes with pyridine containing substrates is feasible, although clearly further optimisation would be required.

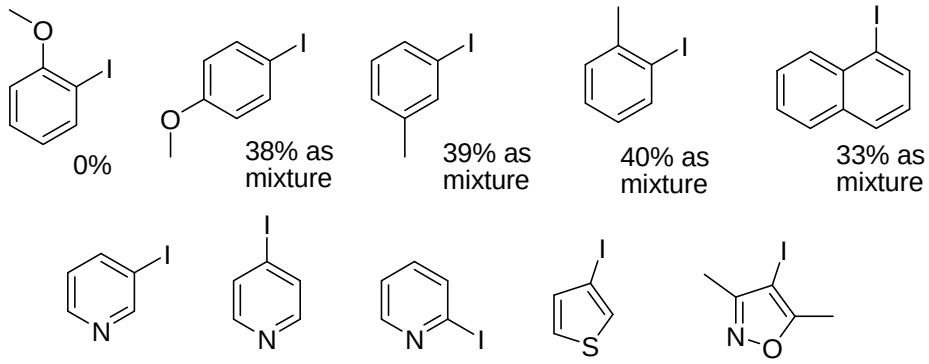


Figure 3.5 Some electron rich and heteroaromatic iodides did not participate in the three component Heck reaction or yielded inseparable mixtures.

Although a range of functional groups were well tolerated, it was not surprising to find that neither 4-iodophenol nor 4-iodoaniline yielded a successful three component coupling: the latter yielded mono-phenylated iodoaniline **208** as the sole product whereas the former also underwent nucleophilic addition to benzyne but in addition a two-component Heck coupling took place, thus all three components were incorporated though not in the desired arrangement **207** (Figure 3.6).

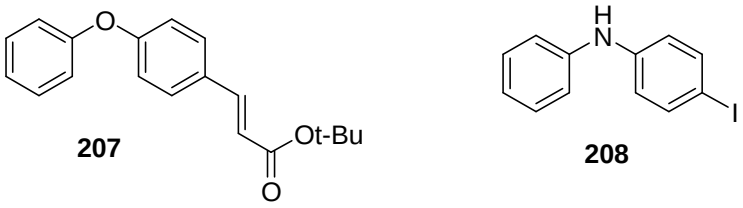


Figure 3.6 Aryl iodides containing a nucleophilic group did not participate in a 3CC

Where mixtures of 2CC and 3CC were difficult to separate by chromatography, cleavage of the ester with triflic acid in DCM followed by recrystallisation was considered as a possibility for purification, as this had proven efficient for the benzyl bromide 3CC products. Although in some cases a degree of separation was possible, a significant amount of product was lost, meaning yields were unacceptably low. Thus the only case where this proved to be a useful strategy for separation of two and three component coupling product was when using 3-iodoanisole.

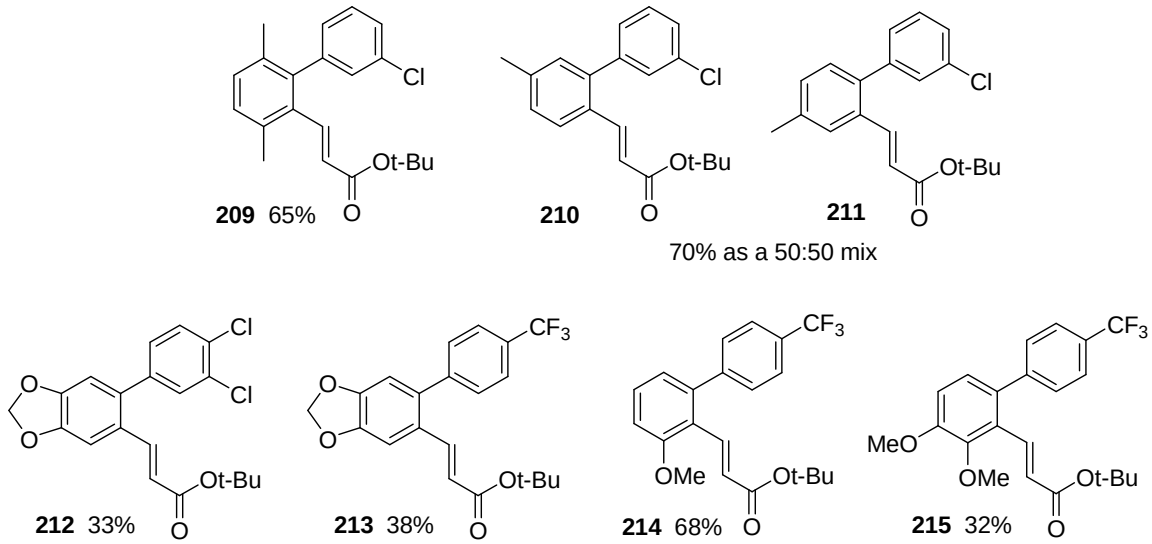


Figure 3.7 Substituted arynes can be employed in three component coupling

A range of substituted aryne precursors could be employed in the reaction (Figure 3.7). Again, a 50:50 mixture of regio-isomers was obtained using a mono-methyl substituted precursor (**210** and **211**), and the highly substituted (*E*)-3-(3'-chloro-3,6-dimethyl-biphenyl-2-yl)-acrylic acid *tert*-butyl ester **209** was formed in good yield. Electron-rich methoxy substituted precursors could also be used, producing a single regioisomer, although yields with these substrates were lower. This may be due to

either the reactivity of the arynes or their rate of generation being slightly mismatched to the reaction conditions, leading to a larger amount of multi-benzyne containing products. A limited screen of alternate reaction conditions was carried out showing that a slightly reduced temperature for the reactions did give an improved yield (Table 3.9). A screen of alternate phosphine ligands was not carried out, P(*t*–Bu)$_3$ giving a very similar yield to P(*o*-tol)$_3$. Both mono- and di-methoxy substituted arynes produced the same regiochemical outcome, which was assigned by 2D-NMR studies initially, and confirmed for **215** by single-crystal X-ray diffraction of the carboxylic acid (Figure 3.8).

Table 3.9 Lowering temperature improves yields for electron rich arynes

Entry	Temperature	Ligand	Yield (214)	Yield (215)
1	45	P(*o*-tol)$_3$	52	20
2	40	P(*o*-tol)$_3$	68	32
3	35	P(*o*-tol)$_3$	45	no reaction
4	40	P(*t*-Bu)$_3$.HBF$_4$	62	10
5[a]	40	P(*o*-tol)$_3$	52	12

Reactions were carried out using 5 mol% Pd(OAc)$_2$, 10mol% ligand, in 1 mL MeCN for 4 h. [a] 4 additions of 0.5 equiv. aryne precursor were made.

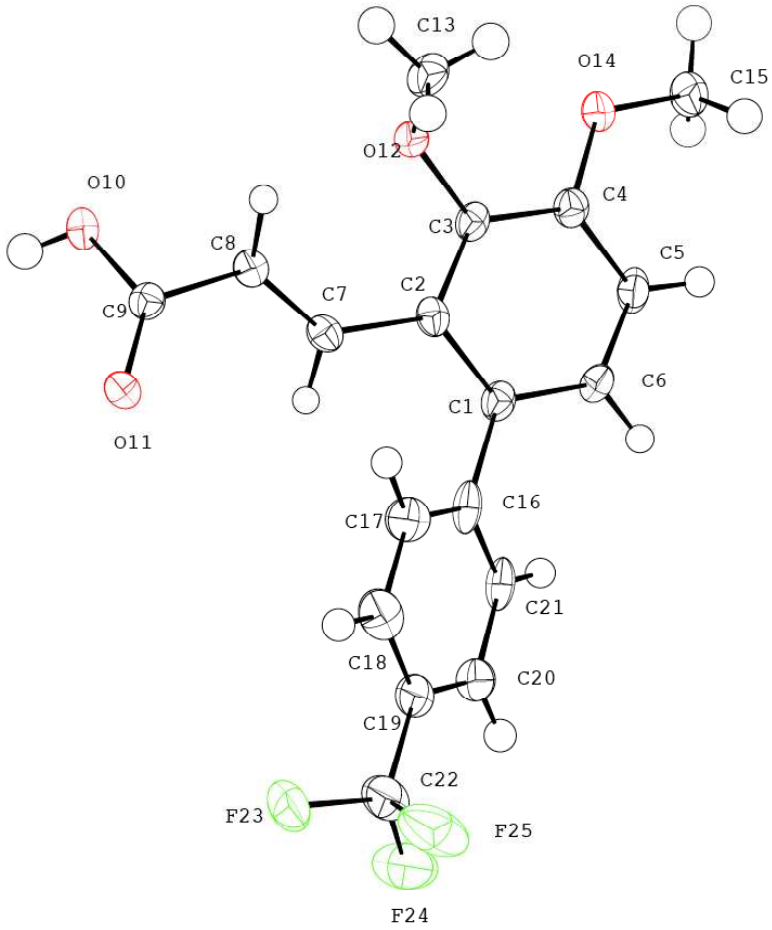


Figure 3.8 X-ray crystal structure of (*E*)-3-(5,6-Dimethoxy-4'-trifluoromethyl-biphenyl-2-yl)-acrylic acid (acid of **215**), which confirms the regiochemical outcome of the three component Heck reaction

Unlike the previous Heck coupling it was possible to move away from acrylate esters as the Heck acceptor (Figure 3.9). Enamides *N*,*N*-dimethylacrylamide and 1-morpholinoprop-2-en-1-one afforded high yielding reactions, as did the electron rich *p*-methoxy styrene. Other styrenes did not offer similar success, probably due to purification issues, however combining a polar aryl iodide with a non-polar styrene did allow for the isolation of **221** in a respectable 43% yield. Hex-1-en-3-one was also applied successfully, although in a lower 38% yield (**219**). These results clearly demonstrate the power of this reaction to rapidly generate a wide range of structural diversity in a single operation.

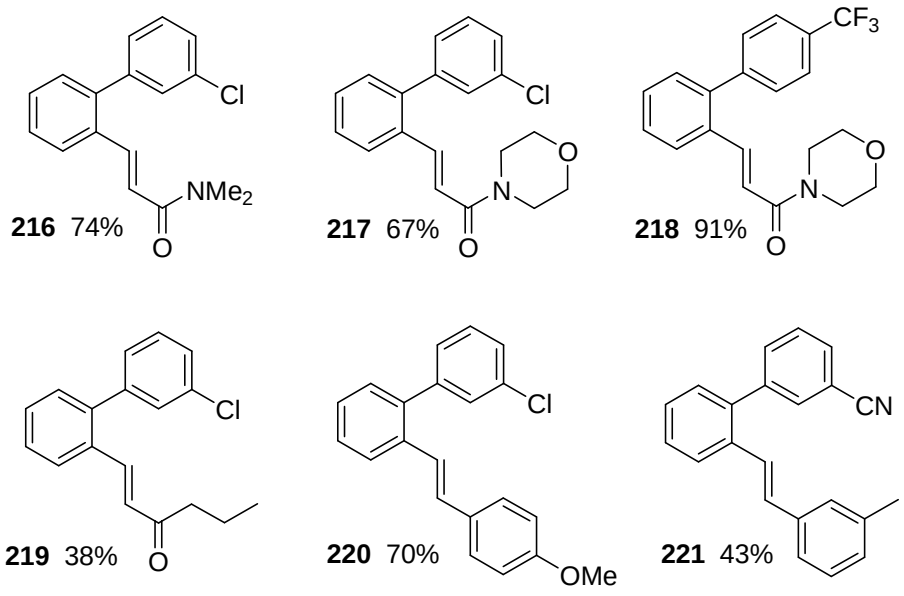


Figure 3.9 Results using alternative alkenes

With a successful reaction in hand the application of aryl bromides to this chemistry was reexamined. Neither electron-rich nor electron-poor aryl bromides could be efficiently employed in the reaction, yielding neither 2CC nor 3CC under the optimized reaction conditions, using a variety of phosphine and NHC ligands. Similar to the allyl-type systems, reactions did not proceed in the absence of fluoride; substituting Cs_2CO_3 for CsF with other parameters unchanged yielded only starting materials, showing again that benzyne is likely involved in the reaction, although the absence of two component Heck product under such conditions is perhaps surprising. It is also worth emphasising that a number of potential side reactions were not observed. Recent work from the groups of Larock and Gallagher have demonstrated that upon oxidative addition of *o*-halobiaryls to palladium a 1,4-palladium shift can occur, leading to the *o*'-derived products.[165, 166] Such regioisomeric products were not observed in this case, which is probably due to the intramolecular C-H activation being suppressed at lower temperatures. Moreover there was no evidence of benzyne-benzyne-alkene trimerisation, a common by-product during reactions of benzyl bromides, which was also reported in good yields utilising the $Pd(OAc)_2$/P(*o*-tol)$_3$ catalyst system by Peña and coworkers.[108] Indeed using the conditions from

their paper ($Pd(PPh_3)_4$, 1:1 MeCN/Toluene, 60 ºC, 16 h), no dihydrophenanthrene products were observed.

3.4 Mechanistic Investigations

During the course of these investigations a number of interesting observations have been made that may begin to yield some insight into mechanistic aspects of the reaction.

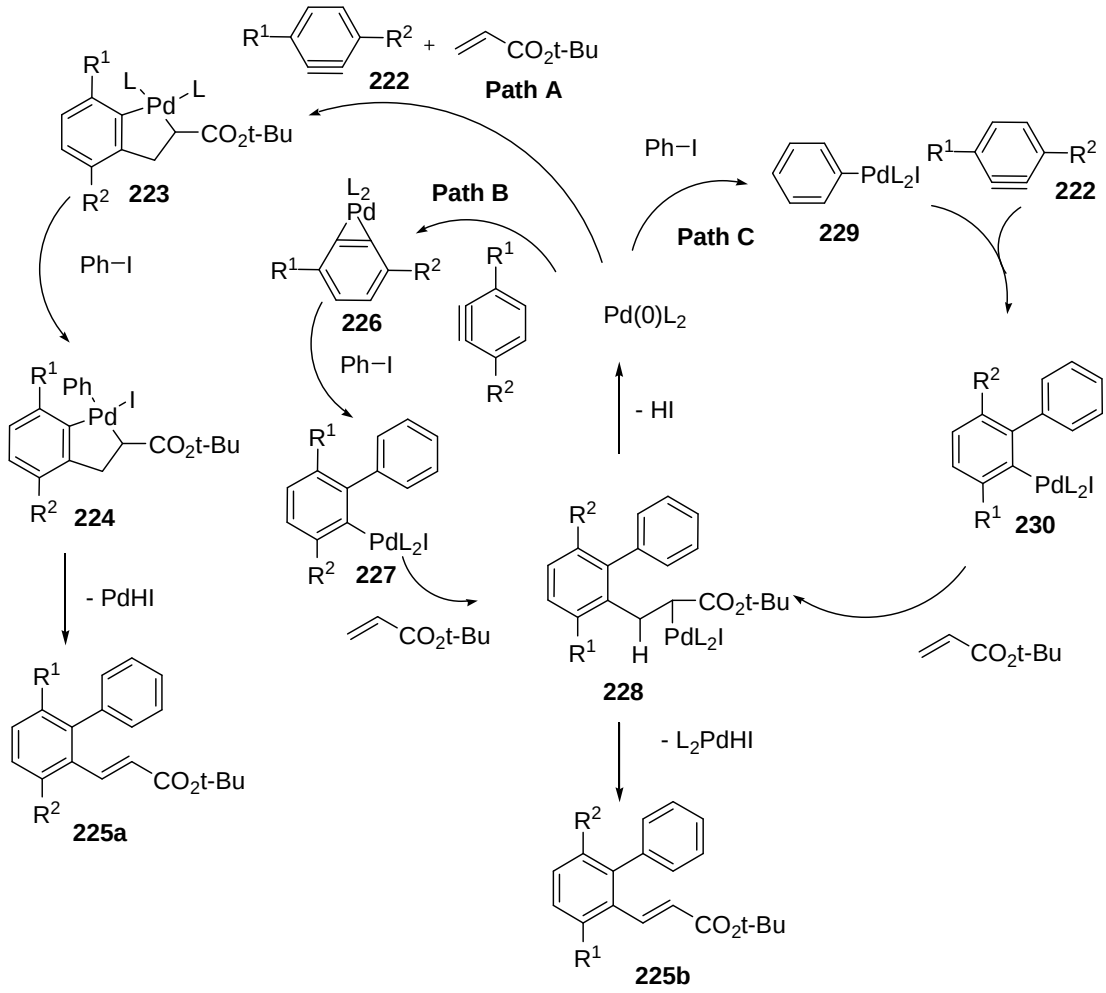


Figure 3.10 Potential mechanistic pathways for three component coupling

A discussion of the mechanism might begin with an examination of the sequence of coupling steps. Three potential mechanistic pathways exist for this reaction; two of

these begin with coordination of benzyne to the palladium, forming an η^2-palladium species (Paths A and B, Figure 3.10), or alternatively oxidative addition of the aryl iodide may begin the reaction sequence.

Pathway A shows benzyne coordination occurring in concert with the acrylate, forming a palladacycle **223** which has been proposed as an intermediate by both Cheng and Peña in their recent work.[108, 127] Oxidative addition of the aryl iodide then forms a Pd(IV) species, precedented in the norbornene shuttle work of Catellani and Lautens using analogous palladacycles.[26, 167] Reductive elimination and β-hydride elimination would subsequently yield the observed products. If this mechanistic pathway is in operation it would be expected that alkyl iodides would also be able to undergo facile oxidative addition to the palladacycle, as demonstrated previously.[24] Under the reaction conditions no coupling of *n*-butyl iodide or *iso*-butyl iodide was observed, nor was *tert*-butyl 9,10-dihydrophenanthrene-9-carboxylate (**129b**), from interception of the palladacycle by benzyne, formed. Exclusive formation of **214** and **215** from reaction of 3-methoxy- and 3,4-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**257** and **258**) also rules out the cyclisation pathway A. Inductive and dative effects provided by the methoxy group would be expected to be highly selective for cyclic intermediate **223**, having R^1 = OMe, subsequently forming the alternative regioisomer (**225a** having R^1 = OMe) than the one which is observed.

Utilising substituted aryne precursors pathways B and C (Figure 3.10) would be expected to yield the same regioisomeric products, thus an alternative method to distinguish between them was sought. In order to demonstrate which of the two mechanisms may be in action attempts were made to prepare the organopalladium species formed after the first steps in each pathway, namely a palladium-benzyne species **226** and an aryl-palladium species **229**. The latter of these is relatively well documented, in particular with triphenylphosphine as the ligand. These compounds are prepared in a straightforward manner by treating $Pd(PPh_3)_4$ with an aryl iodide at room temperature in DCM. Although triphenylphosphine had been found to be ineffectual in the 3CC, it was shown in the case of benzyl bromides that a similar

species could be employed stoichiometrically, despite $Pd(PPh_3)_4$ also proving a poor catalyst for this system (Figure 2.21).

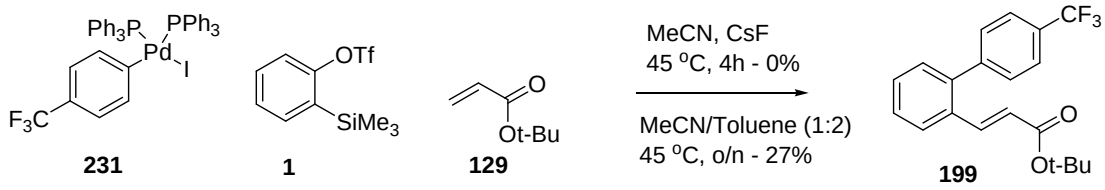


Figure 3.11 Stoichiometric palladium complex used in 3CC

Results using the preformed aryl palladium species **231**, formed by reaction of the aryl iodide with $Pd(PPh_3)_4$, proved inconclusive. No 3CC product was produced under the reaction conditions, however prolonged heating for 24 hours in mixed solvents (to slow benzyne generation rate) did produce a low 27% yield of the desired compound **199** (Figure 3.11). Similarly low yields were observed by Larock during his investigation into the mechanism of triphenylene formation from biaryliodides and benzyne (Figure 3.12).[121] Where the catalytic reaction yielded 92%, the pre-formed palladium species **232b** produced only 22% of **233**, with the phosphine ligand being the only change in the reaction conditions. The author does not provide an opinion on what causes such a drop in yield.

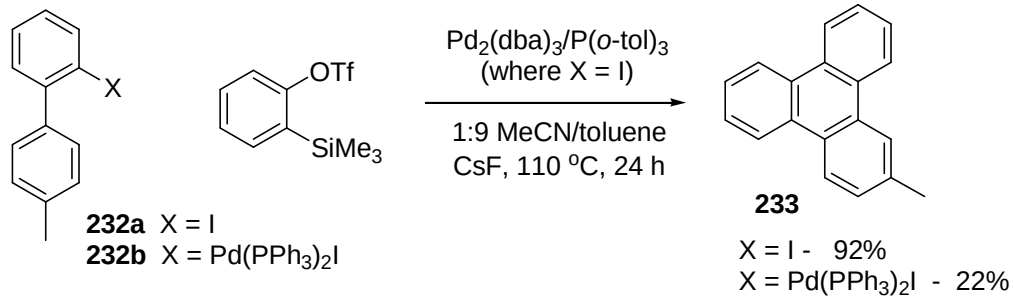


Figure 3.12 Formation of substituted triphenylenes through reaction of catalytically and stoichiometrically palladium activated biarys with benzyne

Although these results suggest that oxidative addition followed by carbopalladation of benzyne is not the prevalent mechanism in the reaction, it could also be postulated that the ligand plays an important role. As P(*o*-tol)$_3$ is well reported to form dimeric

palladium species, with fewer ligands coordinated to palladium than in the case of PPh_3, then this could be crucial for effective carbopalladation of benzyne. Aryl-palladium species with P(*o*-tol)$_3$ as ligands are rare in comparison to the PPh_3, and their synthesis is more complex. Hartwig and coworkers have been responsible for much of the research in this area, however it was not possible to isolate any of the desired complex utilising their procedures.[168] In the majority of cases crystals were not recovered, and the residue displayed numerous ^{31}P and ^{19}F peaks in the respective NMR spectra. Attempts to synthesise the Pd(0) species, Pd[P(*o*-tol)$_3$]$_2$, were also fruitless. As an ArPdI-P(*o*-tol)$_3$ species was not successfully generated, P(*o*-tol)$_3$ was added to the reaction of **231** in an attempt to promote ligand exchange. This had no effect on the reaction outcome.

Pathway C (Figure 3.10) could be viewed as rather improbable due to the requirement of two highly reactive intermediates to be reacting with one another. These reactive species would be present in only very low concentrations at any one time, whereas a stoichiometric amount of alkene is also present which itself should be highly reactive towards the aryl-palladium intermediate. Pathway B, therefore, begins to look the more attractive of the proposed mechanisms and thus studies towards determining the plausibility of such a mechanism were also undertaken.

Benzyne-palladium complexes **(226)** that would be postulated from Pathway B have not been previously reported, however similar species have been isolated using other metals such as nickel[147] and zirconium.[96] Work in the area reports forming dimeric species, generally incorporating two molecules of benzyne coordinated to one or two palladium atoms.[147] It is likely that on the way to these species a palladium-benzyne complex is formed, thus it may be possible to generate *in situ* using a similar methodology. For example, by generating an aryl-palladium species containing an *ortho*-boronic ester (**235**), the required benzyne-palladium species **226** could then be generated by addition of a strong base, KO*t*Bu, to the reaction (Figure 3.13).

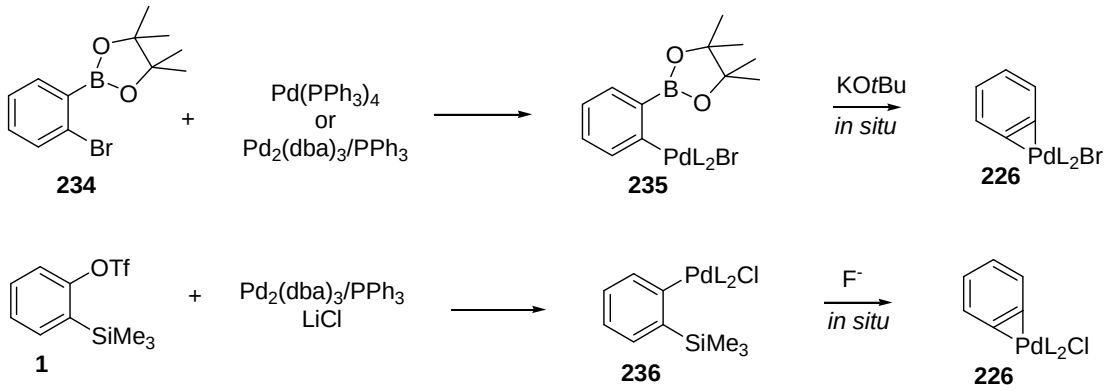


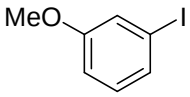
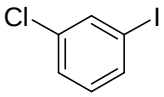
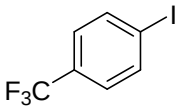
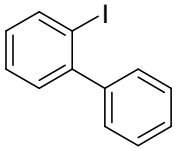
Figure 3.13 Potential methods of generating a Pd-benzyne complex *in situ*

Despite numerous attempts it was not possible to generate the required palladium complex from the aryl bromide **234**. Using the reported conditions employing $Pd_2(dba)_3$ or by heating with $Pd(PPh_3)_4$ only trace amounts of an aryl-palladium complex could be observed using ^{31}P NMR, and this was irreclaimable. There have been few reports of forming aryl-palladium species using aryl triflates, however this was also attempted employing 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1**. The aryl-palladium complex (**236**) that would have been formed could potentially generate the required benzyne-palladium species upon treatment with fluoride, however synthesis again failed.

It would be expected that under the developed reaction conditions two-component Heck coupling would be fast, therefore selectivity over three-component coupling is difficult to achieve. Control experiments in the absence of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate tell a very different story, yielding just 12 – 22% of the desired Heck product after 4 hours (Table 3.10). Allowing the reaction to run for an extended period of 24 hours significantly increases the yield to greater than 90%. This unexpected result suggests that the presence of benzyne significantly increases the reaction rate. If oxidative addition – Heck reaction is slow, it seems unlikely that oxidative addition – aryne carbopalladation – Heck reaction would be substantially faster, suggesting that the aryne is having a important effect on the catalytic pathway in regard to 2CC versus 3CC coupling. Whether this is through the formation of the η2-metallocyclopropene or through another mechanism is still unclear. For example, Herrmann reported that for palladacyclic species, no reaction between aryl halide and

palladium is observed in the absence of an olefin, thus another hypothesis would be that benzyne is activating the catalyst in some way.[163] Again this result suggests that Pathway C is not the prevalent mechanism.

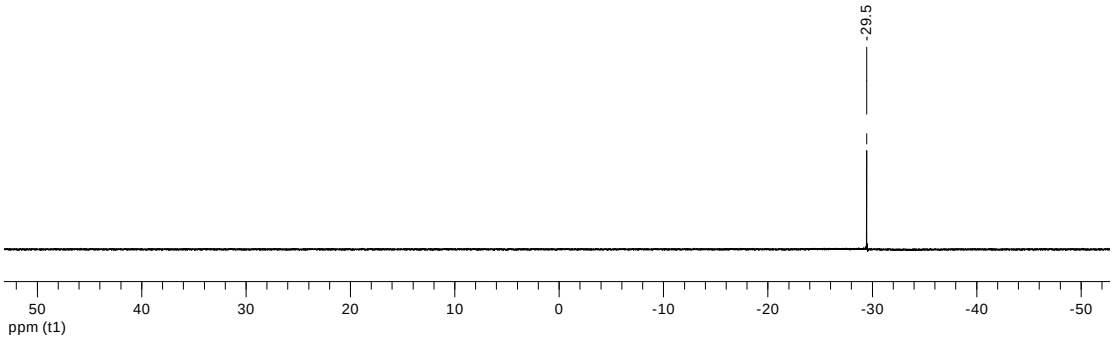
Table 3.10 2CC reactions in the absence of benzyne precursor

Entry	Aryl Iodide	Yield in 2CC[a]	Yield in 3CC[b]
1		22	62
2		14	73
3		13 (91[c])	86
4		0	nd

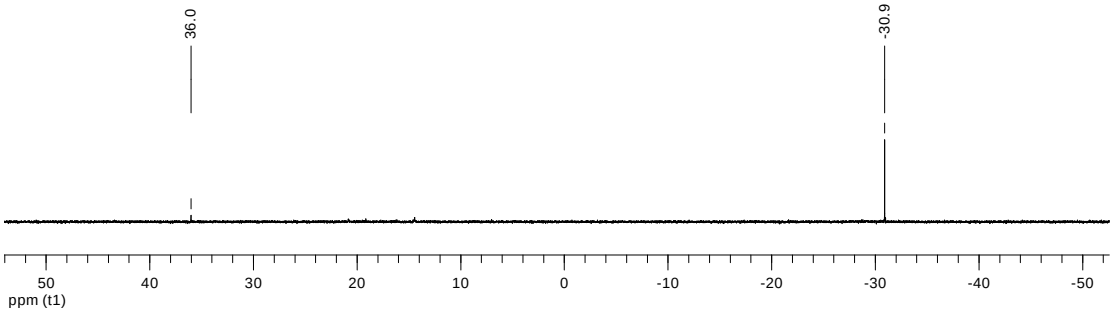
[a]Reactions carried out as previously over 4 h with the omission of aryne precursor **1**. [b]Reaction conditions as Figure 3.4 [c]Yield after 24 h. nd = not determined.

As the above results gave some fascinating insight into the importance of benzyne in the Heck reaction, it was felt that further mechanistic studies were required. As it had not been possible to synthesise suitable palladium species, NMR studies were used to monitor the progress of the reaction, and in particular the palladium species present through ^{31}P NMR. Utilising stoichiometric palladium/ligand in deuterated acetonitrile as solvent, the species present were monitored after addition of each of the substrates. The relevant NMR spectra are shown below.

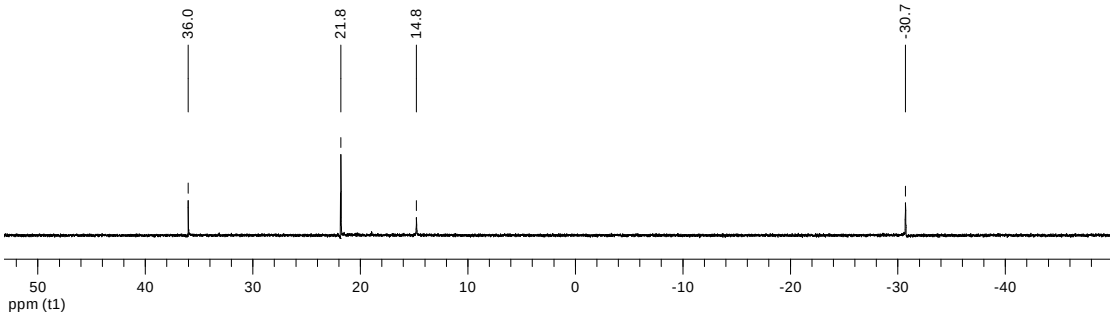
P(*o*-tol)$_3$



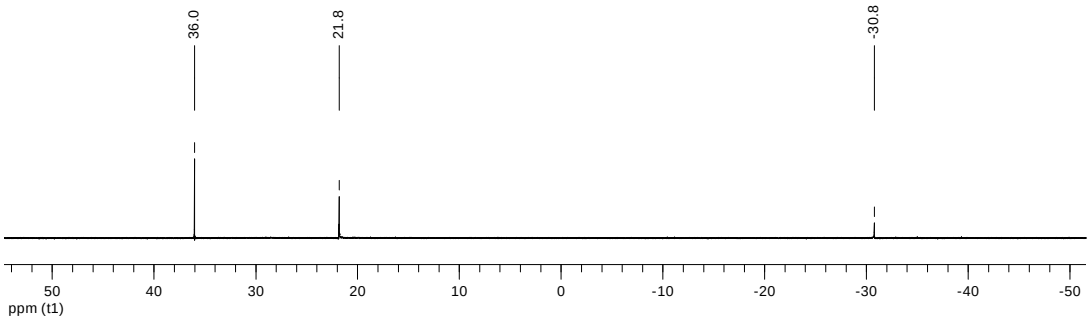
Pd(OAc)$_2$ and P(*o*-tol)$_3$ after stirring for 30 mins at 45 ºC in CD$_3$CN with CsF



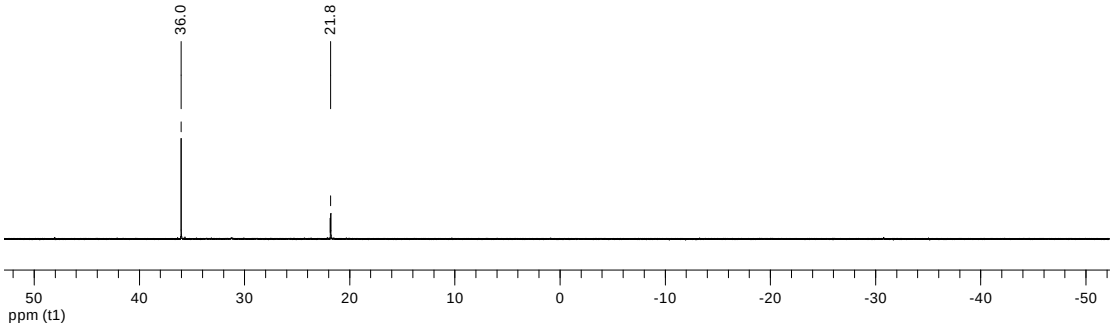
Addition of benzyne precursor and stirred for 90 mins



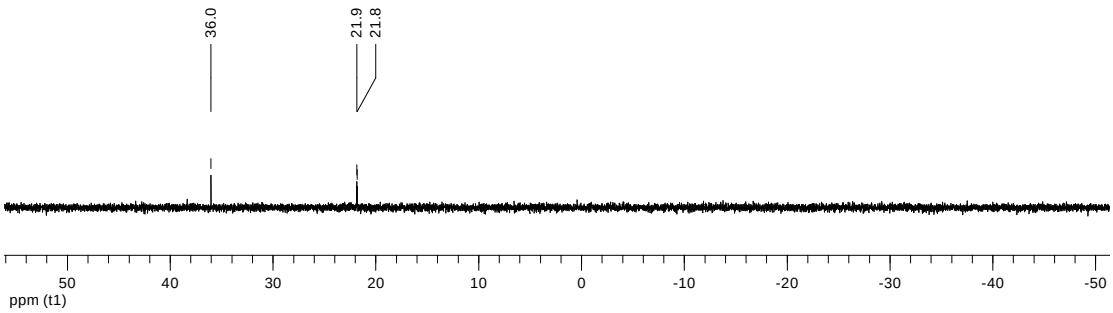
Addition of 3-chloroiodobenzene and stirred for 90 mins



***tert*-butyl acrylate added and stirred for a further hour.**



Catalytic reaction after 20 mins



Initially sequential addition of benzyne, aryl iodide and then acrylate to the palladium ligand system was examined. Despite stirring for 30 mins at 45 ºC a combination of $Pd(OAc)_2$, P(*o*-tol)$_3$ and CsF shows little if any change in the ^{31}P NMR from P(*o*-tol)$_3$ alone. Normally, on formation of a palladium-phosphine complex, a significant shift in the NMR is observed, for example $Pd[P(o\text{-tol})_3]_2$ displays a resonance at -6.7 ppm.[168] This supports the conclusions of Amatore that a Pd(0) species is not formed spontaneously from reaction of $Pd(OAc)_2$ with P(*o*-tol)$_3$.[169] However, Herrmann reports that palladacycle formation occurs after only 5 minutes at 50 ºC in toluene, thus it is surprising that in this solvent no palladium complex is observed.[163]

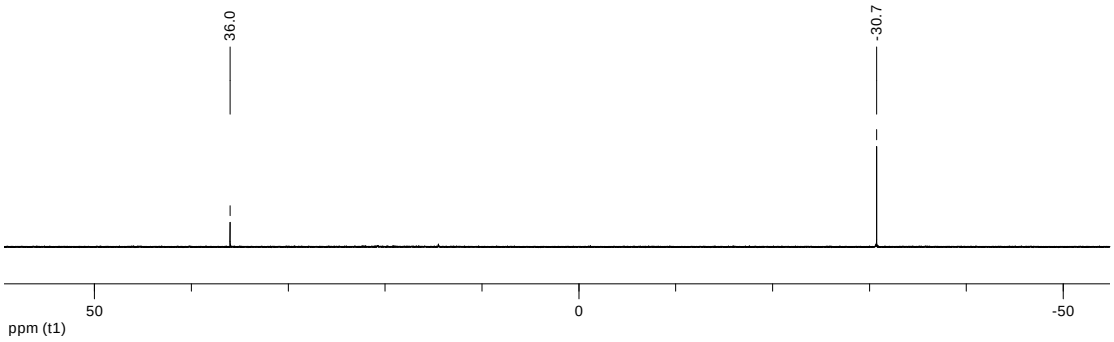
Benzyne precursor was then added and the reaction stirred for a total of 90 minutes (at which point none of the benzyne precursor remained by ^1H NMR). Observations over this time period showed the development of a clear peak at 21.8 ppm, along with smaller peaks at 36.0 and 14.8 ppm. The latter of these corresponds to the reported value for the phosphine oxide. The other two peaks fall almost equidistant

from the values reported by Hartwig for the dimeric species $[Pd[P(o\text{-}tol)_3]ArBr]_2$, which range from 25.8 to 30.3 ppm.[168] Interestingly, he reports either a broad singlet or two peaks for these dimers, which was also observed for the peak at 21.8 ppm. Mixtures of P(*o*-tol)$_3$ with Pd_2dba_3 (or of $Pd[P(o\text{-}tol)_3]_2$ with dba) yield a poorly characterized complex containing both P(*o*-tol)$_3$ and dba, giving a phosphine resonance at 20 ppm. Both of these factors suggest that the peak at 21.8 ppm corresponds to a palladium-benzyne complex, which may be dimeric. However, during attempts to prepare η^2-palladacycles with benzyne, Retbøll and coworkers observed a new phosphine peak at 41.5 ppm which they assigned to the η^2-complex.[147] The peak at 36.0 ppm may correspond to palladacycle formation, the reported value (in DMF) being around 34 ppm.[163]

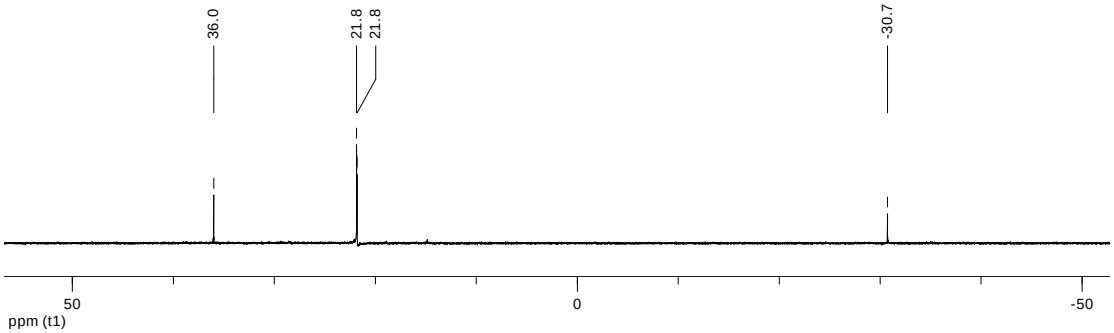
3-Chloroiodobenzene (1 equiv.) was then added to the reaction, which was again monitored over a period of 90 mins. During this time the ratio of the three main peaks altered such that the peak at 36.0 ppm became the largest, with both the peaks at 21.8 and -30.8 ppm decreasing, thus suggesting the peak at 36 ppm may represent an η^1-linked aryl-palladium species. Following addition of *t*-butyl acrylate, the peak at -30.8 ppm is consumed, with the peak at 36.0 ppm increasing further in size. ^{1}H NMR shows that 3CC product is being produced in the reaction, illustrating that such a process is viable. To show that similar species are formed in the catalytic process a reaction carried out in CD_3CN was sampled after 20 minutes, showing the same peaks at 36.0 and 21.8 ppm as previously observed.

These results were also compared with the alternate addition sequence, where aryl iodide is allowed to react first with stoichiometric palladium and ligand before addition of benzyne and *t*-butyl acrylate.

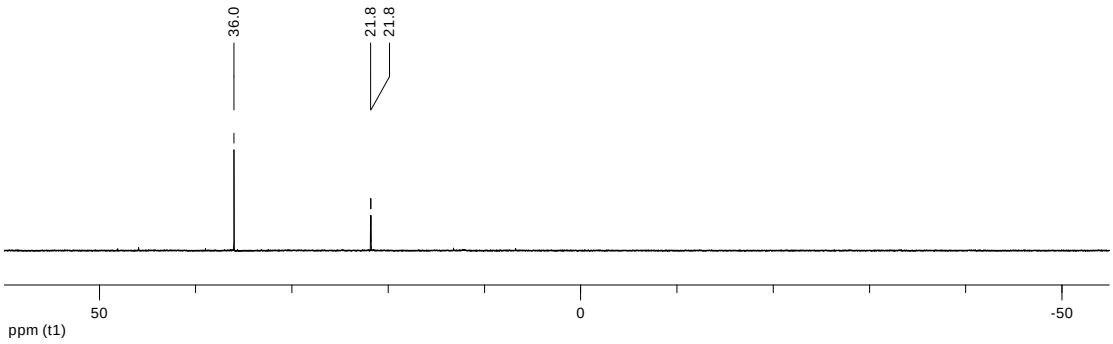
Addition of 3-chloroiodobenzene and stirred for 120 mins



2-(trimethylsilyl)phenyl trifluoromethanesulfonate added and stirred for 90 mins



***tert*-butyl acrylate added and stirred for a further hour.**



In this case it was observed that 2 hours stirring at 45 ºC was required to see a significant change in the phosphine or proton NMR after addition of the aryl iodide, with the appearance of a peak at 36.0 ppm that had been observed beforehand. Treatment with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate yields a similar distribution of peaks to those previously recorded, treatment with acrylate then leading to an increase in intensity of the peak at 36.0 ppm, with the simultaneous loss

of the -30.8 ppm peak. Proton NMR confirms that 3CC is occurring, in approximately a 5:2 ratio with 2CC.

^{31}P NMR demonstrated that benzyne may react with palladium and P(*o*-tol)$_3$, producing a new species, although the nature of this species has not been ascertained. As the entire benzyne precursor was consumed prior to addition of the aryl iodide, 3CC produced from this reaction must be due to a trapped benzyne species, free benzyne not surviving in solution for extended periods of time. It is possible, however, that addition of benzyne to palladium is reversible, releasing benzyne into solution and hence achieving the observed results. The NMR study does back up the observation that 2CC is slow under the reaction conditions, oxidative addition to form an aryl-palladium species being sluggish. On the whole, these reactions support the theory that a benzyne-palladium complex may be the initial species in the catalytic cycle, however the interactions between the reactive species and their affects on both the rate and outcome of the reaction are not trivial and thus a great deal of further work is required to tease apart the intricacies of the mechanism.

3.5 Applying the methodology

This three-component Heck coupling has the potential to prove its worth in the rapid synthesis of both small molecule targets and natural products. In a related series of prostanoid receptor antagonists to those seen previously, three component coupling can again be used for the rapid and efficient synthesis of pharmacologically active compounds.[170, 171] A three-stage process involving palladium catalysed benzyne coupling, followed by deprotection of the ester and amide bond formation gives an overall yield of 60% for the EP3 antagonist **238** and would again be amenable to library synthesis (Figure 3.14).

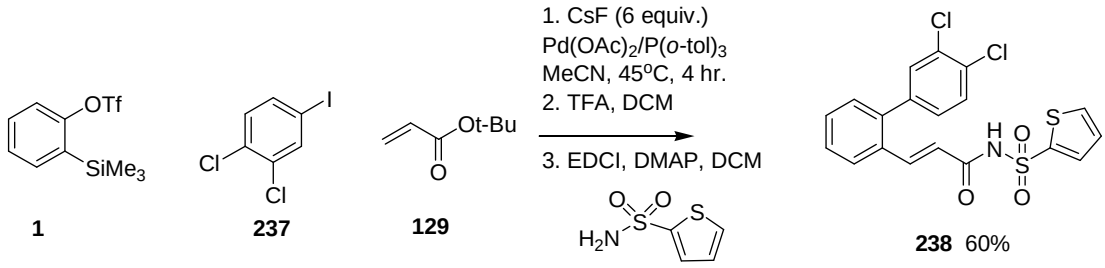


Figure 3.14 Synthesis of EP3 prostanoid receptor antagonist

As well as being applicable to the synthesis of a range of pharmacologically interesting compounds, such as the diacylglycerol acyltransferase inhibitor recently reported by Roche,[172] cathepsin K inhibitor under investigation by Merck for the treatment of osteoporosis[173] and melanocortic receptor 4 antagonist published by Taisho[174] (Figure 3.15), the three component coupling could also be useful for synthesising natural product targets. For example, Riccardin C, a cytotoxic compound isolated from the liverwort species *Riccardia hemisphaerica*,[175] could be generated from the union of a suitably substituted aryl iodide and styrene with benzyne. This could be employed in a three component fashion, ring synthesis then being accomplished via a Wittig reaction for example, or could be used in a two-component fashion, the intramolecular Heck reaction forming the macrocycle (Figure 3.16).

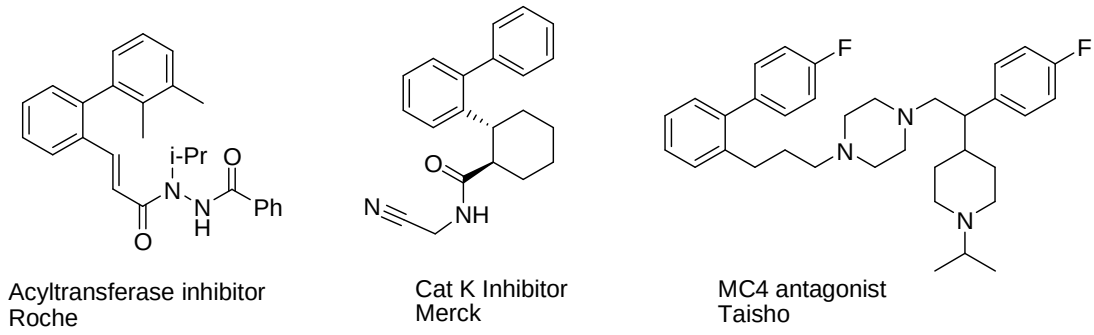


Figure 3.15 Other medicinal chemistry targets that could be accessed *via* three component coupling

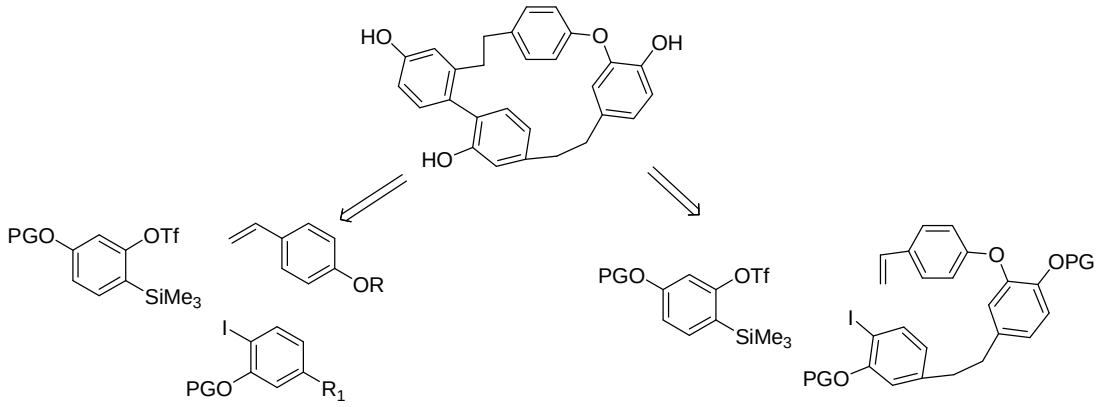


Figure 3.16 Possible synthetic strategies for the synthesis of Riccardin C

3.6 Expanding the methodology - four-component coupling

It could be proposed that the developed three component coupling could be expanded further to incorporate a fourth component, namely carbon monoxide, and hence lead to the formation of three carbon-carbon bonds in a single operation (Figure 3.17).

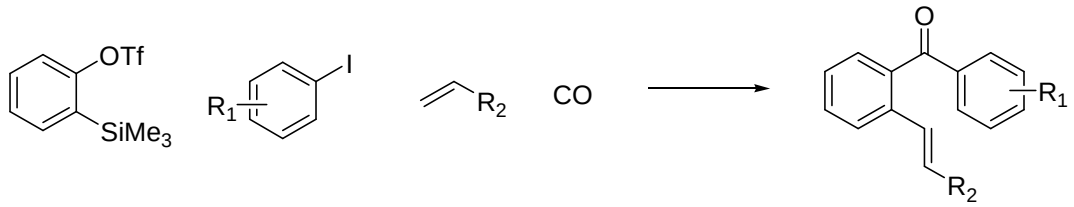


Figure 3.17 Proposed four component coupling with carbon monoxide

The facile insertion of carbon monoxide into an organo-palladium bond was reported as early as 1974, initial reactions involving nucleophilic attack of water or an alcohol on the acyl palladium species generated.[9] This has since been expanded to reaction of the acyl palladium with a full range of organometallic reagents along with its participation in intramolecular Heck reactions, where the initial organohalide contains a suitable double bond. As reaction of carbon monoxide with organopalladium species is both facile and fast, it should be possible to incorporate such a reaction into the present sequence, giving a four component coupling.

Precedence for such a coupling also comes from the work of Murai, who demonstrated that the aryl palladium species formed after reaction of allyl acetate and benzyne could be intercepted with carbon monoxide, followed by cyclisation (Figure 1.58).[119]

Initial reactions were carried out under a carbon monoxide atmosphere, using a CO filled balloon. At atmospheric pressure (of CO), aryl iodide was recovered unreacted. Although the benzyne precursor was consumed, the species formed was not identified though it would be presumed to form anthraquinone species as reported by Murai.[119] Where the CO was bubbled directly into the reaction mixture the benzyne precursor remained unreacted.

Molybdenum hexacarbonyl ($Mo(CO)_6$) has been found to be a suitable alternative to CO gas in palladium catalysed couplings, and has the advantage of being easy to handle.[176] Under the developed Heck reaction conditions $Mo(CO)_6$ used in a range of stoichiometries (0.5 – 2 equiv.) was unsuccessful at promoting four component coupling, leaving the benzyne precursor untouched after 4 hours at 50 ºC. A screen of alternate reaction conditions for either CO source was not carried out, and this would certainly be a worthwhile exercise.

4 Three component coupling – the Buchwald Reaction

After the success achieved using alkenes in the Heck reaction, forming two carbon-carbon bonds in one step, outlets to further expand the chemistry were sought. Application of similar methodology to the Buchwald reaction would lead to the formation of a carbon-carbon and carbon-heteroatom bond in a single step, producing interesting molecular architecture (Figure 4.1).

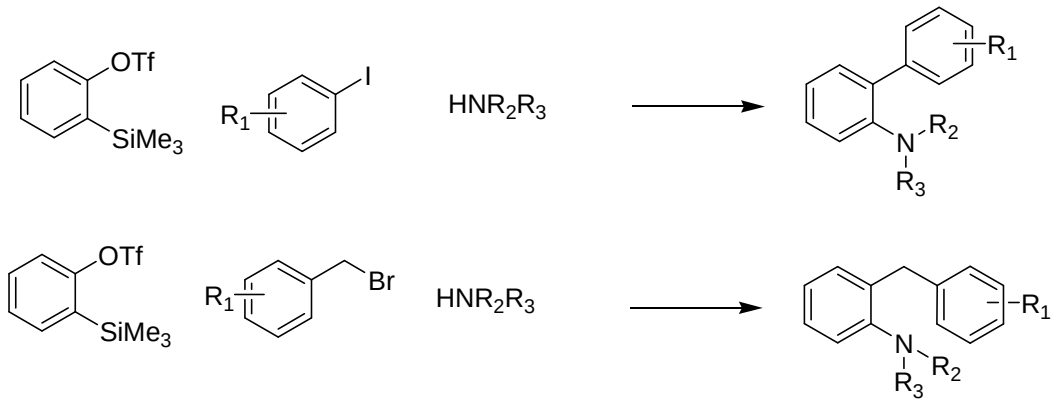


Figure 4.1 Examples of a three component Buchwald reaction

The Buchwald reaction will likely prove an even tougher test than the Heck reaction. Benzyne is a powerful electrophile; it is well known, and widely reported, that benzyne reacts with amines to form arylated amines, constituting some of the earliest experiments with benzyne, and recently being reported to be an efficient way of arylating a range of amines, amides and sulfonamides.[75, 77] Similar to the Heck reaction, there may be problems with two-component coupling, and when using alkylating agents such as benzyl bromides there may also be issues with alkylation of the amine or quaternisation of any products generated. A related reaction sequence has been achieved by Larock, who used a nucleophilic attack on benzyne by *ortho*-iodoanilines followed by a palladium catalysed reaction to form the two bonds in one pot (Figure 1.42), however the palladium catalysed coupling in this case is an intramolecular direct arylation.[78, 79]

4.1 An introduction to the Buchwald reaction

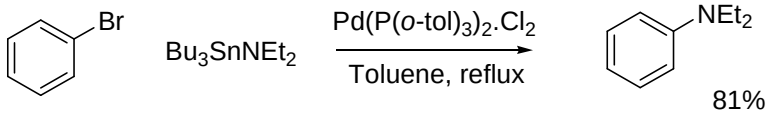


Figure 4.2 Original palladium catalysed coupling of an aryl bromide with aminostannanes

The Buchwald, or Buchwald-Hartwig reaction was actually introduced by Migita in 1983, who was the first to report the palladium catalysed formation of aryl amines from tin amides and aryl bromides (Figure 4.2).[177] This work went unreferenced for a decade when it was simultaneously followed up by the groups of Hartwig[178] and Buchwald,[179] who examined the mechanism and expanded the reaction scope respectively. Again in quick succession Buchwald and Hartwig published methods for a tin-free reaction, utilising a strong base to deprotonate the amine-palladium complex and making the reaction more attractive for industrial applications.[180, 181] Over the last decade both groups have focussed on ligand development to allow for a wider range of substrates to be used under milder reaction conditions, bulky mono- and bidentate phosphines being reported by both groups to be optimal. Alternative nucleophiles, such as alcohols, thiols and carbanions can also be used in the reaction, joining the wide range of aliphatic and aromatic primary and secondary amines and ammonia equivalents that have also been reported (Figure 4.3).[11, 182, 183]

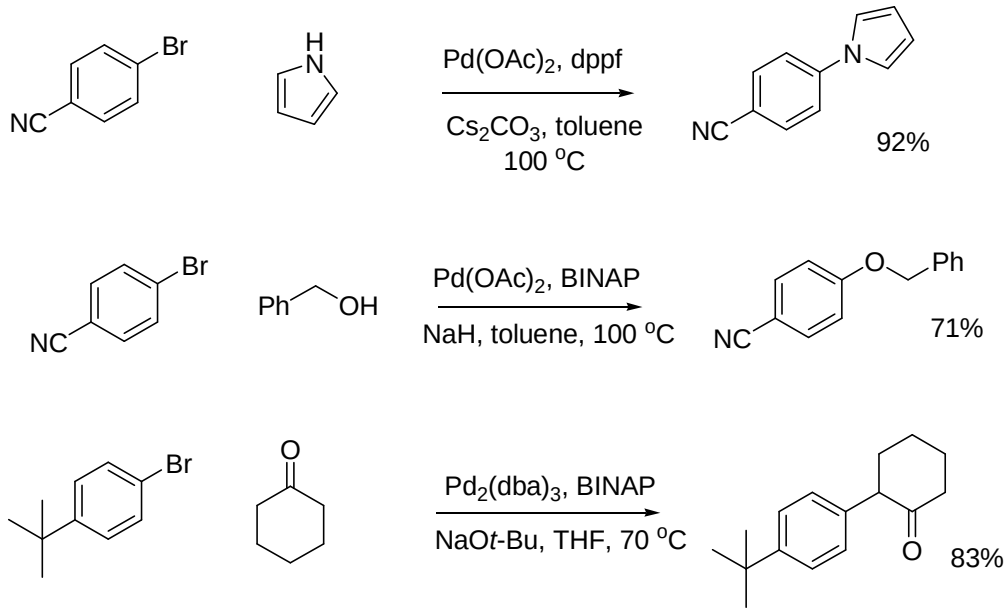
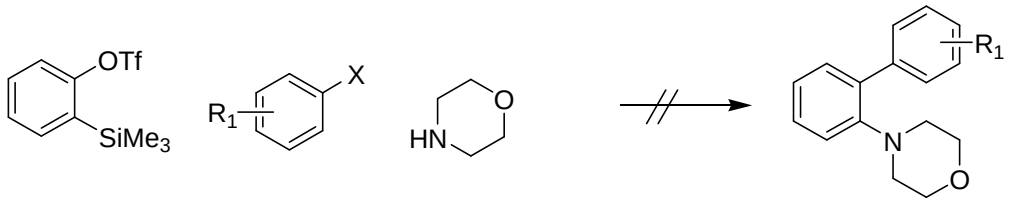


Figure 4.3 Some examples of the Buchwald-Hartwig reaction

4.2 Three component coupling using aryl halides

Initially attempts were made to couple benzyne with aryl halides and secondary aliphatic amines. Morpholine was chosen as it is less nucleophilic than some other commonly used amines and this should hopefully reduce the rate at which it reacts with benzyne. Using a range of palladium sources and ligands, in a variety of solvents and at a range of temperatures there was no evidence of three component coupling (Table 4.1). Phenyl morpholine was the main product in all cases and could be isolated in yields of up to 98%. The reaction between benzyne and the amine was so rapid that in no instance was a 2CC between the aryl halide and morpholine observed. No further work was performed on this system, however success may come from examining alternative amines, perhaps combining this with a survey of bulky phosphine ligands.

Table 4.1 Attempted three component coupling of aryl halides with benzyne and morpholine



Entry	Aryl halide	Catalyst	Base	Solvent	Temp.
1	4-iodotoluene	$Pd(OAc)_2$/dppe		DME	50 °C
2	4-iodotoluene	$Pd(OAc)_2$/dppe	Cs_2CO_3	DME	50 °C
3	4-iodotoluene	$Pd(OAc)_2$/ P(*t*-Bu)$_3$.HBF_4		DME	50 °C
4	4-iodotoluene	Pd(dppf).Cl_2		DME	50 °C
5	4-iodotoluene	$Pd(OAc)_2$/NHC		DME	50 °C
6	4-iodoanisole	$Pd(OAc)_2$/ P(*t*-Bu)$_3$.HBF_4		DME	80 °C
7	4-iodoanisole	$Pd(OAc)_2$/ P(*t*-Bu)$_3$.HBF_4	Cs_2CO_3	DME	80 °C
8	4-iodoanisole	Pd(dppf).Cl_2		DME	80 °C
9	4-iodoanisole	Pd(dppf).Cl_2	Cs_2CO_3	DME	80 °C
10	4-bromotoluene	$Pd(OAc)_2$/ P(*t*-Bu)$_3$.HBF_4		DME	80 °C
11	4-bromotoluene	$Pd(OAc)_2$/ P(*t*-Bu)$_3$.HBF_4	Cs_2CO_3	DME	80 °C
12	4-bromotoluene	Pd(dppf).Cl_2		DME	80 °C
13	4-bromotoluene	Pd(dppf).Cl_2	Cs_2CO_3	DME	80 °C
14	4-iodoanisole	$Pd(OAc)_2$/ P(*t*-Bu)$_3$.HBF_4		Tol/MeCN[a]	110 °C
15	4-iodoanisole	$Pd(OAc)_2$/ P(*t*-Bu)$_3$.HBF_4	Cs_2CO_3	Tol/MeCN[a]	110 °C
16	4-iodoanisole	Pd(dppf).Cl_2		Tol/MeCN[a]	110 °C
17	4-iodoanisole	Pd(dppf).Cl_2	Cs_2CO_3	Tol/MeCN[a]	110 °C
18	4-bromotoluene	$Pd(OAc)_2$/ P(*t*-Bu)$_3$.HBF_4		Tol/MeCN[a]	110 °C
19	4-bromotoluene	$Pd(OAc)_2$/ P(*t*-Bu)$_3$.HBF_4	Cs_2CO_3	Tol/MeCN[a]	110 °C
20	4-bromotoluene	Pd(dppf).Cl_2		Tol/MeCN[a]	110 °C
21	4-bromotoluene	Pd(dppf).Cl_2	Cs_2CO_3	Tol/MeCN[a]	110 °C

Reactions were carried out on a 0.21 mmol scale with 3 equiv. CsF in 1mL solvent. [a] 2:1 ratio of toluene:MeCN

4.3 Buchwald reaction using benzyl bromides

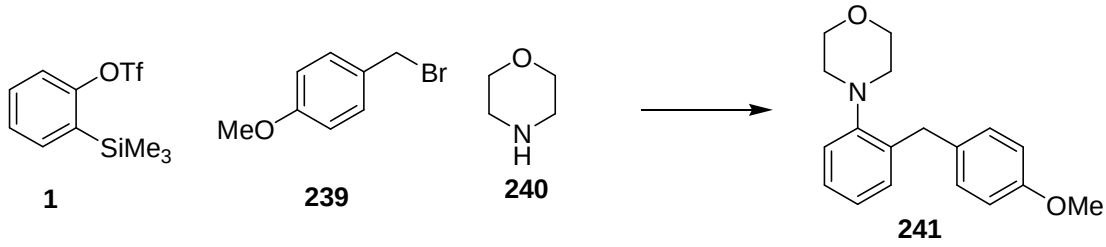
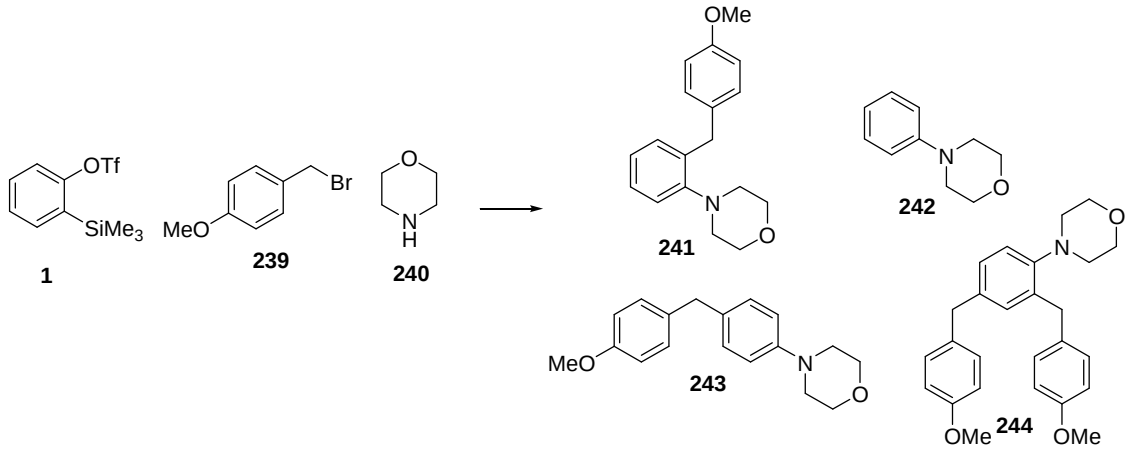


Figure 4.4 Proposed three component coupling reaction

Benzyl bromides were also considered as substrates for a three component Buchwald reaction (Figure 4.4). Along with nucleophilic attack on benzyne, amine alkylation is expected to be facile and, as such, potentially provide another undesired reaction outcome. Although this did not become a particular issue, the reactions proved to be even more complex than initially anticipated, four amine containing products being identified (Table 4.2). Additionally it was observed that three component coupling products were formed in both the presence and absence of palladium, suggesting an alternative mechanism is in operation.

Table 4.2 Three component coupling reactions between benzyne, morpholine and *para*-methoxybenzyl bromide



Entry	Ratio (1:239:240)	Pd Source	Ligand	Solvent	Yield 241	Yield 242	Yield 243	Yield 244*
1	1:1:1	$Pd(OAc)_2$	dppe	DME	3	20	12	0
2	2:1:1	$Pd(OAc)_2$	dppe	DME	4	15	10	0
3	1:1:2	$Pd(OAc)_2$	dppe	DME	0	68	0	0
4	1:1.5:1	$Pd(OAc)_2$	dppe	DME	5	28	24	0
5	1:1.5:1	$Pd(OAc)_2$	dppe	MeCN	9	21	23	7
6[b]	1:1:1	$Pd(OAc)_2$	dppe	DME	5	37	17	nd
7	1:1.5:1	$Pd(OAc)_2$	$P(tBu)_3.HBF_4$	DME	12	39	17	nd
8[c]	1:1.5:1	$Pd(OAc)_2$	dppe	DME	4	20	8	nd
9	1:1:1	-	-	DME	10	19	11	nd
10	2:1:1	-	-	DME	10	5	3	0
11	1:1:2	-	-	DME	0	65	0	0
12	1:1.5:1	-	-	DME	11		11	nd
13	1:1.5:1	-	-	MeCN	9	8	34	16
14	1:1:1	-	-	MeCN	11	16	27	7
15	2:1:1	-	-	MeCN	10	2	9	7
16[b]	1:1:1	-	-	DME	10	35	19	7
17[c]	1:1.5:1	-	-	DME	9	10	14	5

All yields are percentage. Reactions carried out on a 0.21 mmol scale in 1mL solvent with 3 equiv. CsF at 50 ºC overnight. [b]Amine and benzyl bromide stirred at 50 ºC overnight with CsF before adding benzyne then stirred for a second overnight. [c] 75 ºC. *Based on benzyl bromide. nd = not determined.

Over a variety of reaction conditions it was found to be very difficult to optimise the yield of either 3CC product (Table 4.2). The products were also difficult to separate; phenyl morpholine, unreacted 4-methoxybenzyl bromide and 4-(2-(4-methoxybenzyl)phenyl)morpholine eluting together on silica chromatography. Recovery of materials, in particular benzyne containing products, was particularly low, with no conclusive evidence for what was becoming of benzyne was gathered. Crude NMRs indicated only the isolated products, with no other major peaks or signs of polymerisation. It may be that the amine used contained a significant amount of water, benzyne then being consumed in the formation of phenol, or that there are polymeric products being formed that are removed on reaction work-up.

In an attempt to optimise the reaction a number of parameters were varied. Changing the ratio of reactants certainly had an effect on the system; a larger amount of 3CC products were generated when benzyl bromide was in excess. Interestingly, in the presence of an excess of morpholine 3CC products were absent, phenyl morpholine and benzyl morpholine being the only products formed (Entries 3 and 11, Table 4.2). None of the reactions appear to be palladium mediated, with yields of both three-component coupling products being higher when no catalyst is used. Solvent or benzyne generation rate must also factor, with higher yields of the *para*-3CC achieved using MeCN in place of DME (Entries 13 and 14, Table 4.2). Elevated temperature was detrimental to yield where Pd was present but made little difference in its absence. By stirring benzyl bromide with morpholine overnight prior to addition of the benzyne precursor, it could be established that amine alkylation is not occurring under the reaction conditions, benzylated morpholine not being isolated and yields of 3CC not being significantly altered. It is also interesting to note that using 2-bromobenzyl bromide in place of 4-methoxybenzylbromide yielded neither of the three component coupling products, with phenyl morpholine and a small amount of 4-(2-bromobenzyl)morpholine being the only isolated products.

Mechanistically, the reaction is probably not as interesting as it initially seemed. The mixture of *ortho*- and *para*- substituted products points the way to an electrophilic substitution. Friedel crafts alkylation of N-phenylmorpholine, formed from reaction

between benzyne and morpholine, could account for the three observed products. Indeed after treatment of N-phenylmorpholine with 4-methoxybenzyl bromide in MeCN at 50 ºC in the presence of CsF small amounts of the products were observed, although in lower quantities than during 3CC reactions. Formation of the Friedel Crafts products could be enhanced by nucleophilic addition of morpholine to benzyne producing the resonance stabilised anion.

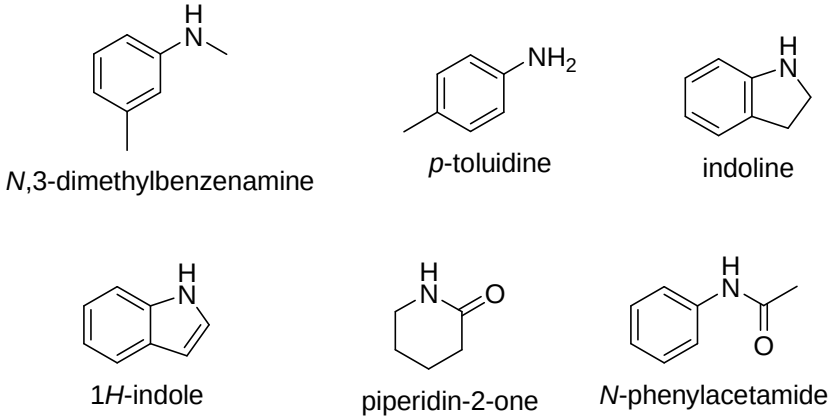


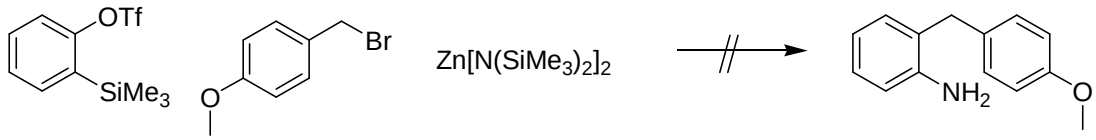
Figure 4.5 Other amines used in the three component Buchwald coupling

A variety of other amines that should be less nucleophilic were also screened for activity in a three component Buchwald reaction under a variety of conditions (Figure 4.5). None of these generated the desired 3CC reaction, with the main products being phenylation or alkylation of the amine. Again a wider screen of ligands along with solvent, base and temperature would perhaps lead to success in this chemistry, however it will probably prove to be extremely difficult to escape from the undesired phenylation.

As secondary amines themselves proved to be too nucleophilic to use in a benzyne Buchwald reaction, giving complex mixtures of products or nucleophilically attacking benzyne, an alternative would be to employ an amine equivalent such as a metalloamide. One which has been used with some success is zinc or lithium bis[bis(trimethylsilyl)amide], an ammonia equivalent.[184, 185] Treatment of the silylamines formed with HCl cleaves the silyl groups to yield the primary aniline as

the coupling product. Use of a species containing silyl groups with an excess of fluoride is perhaps questionable, however as the silylamides are commercially available and the 2CC reactions are reported to give good yields it is a reaction that is certainly worth attempting. It also gives the possibility of a pseudo-three component coupling where the metalloamide adds across the benzyne triple bond, followed by a palladium catalysed cross-coupling reaction between the organometallic and organohalide.

Table 4.3 Screen of reaction conditions for three component Buchwald using zinc trimethylsilylamide as an ammonia equivalent.



Entry	Pd	Ligand	Additive	Solvent	Temp
1	$Pd(OAc)_2$	dppe	LiCl	DME	50
2	$Pd(OAc)_2$	dppe		DME	50
3	$Pd(OAc)_2$	P(*o*-tol)$_3$	LiCl	DME	50
4	$Pd(OAc)_2$	P(fur)$_3$	LiCl	DME	50
5	$Pd(OAc)_2$	P(*t*Bu$_3$).HBF_4	LiCl	DME	50
6	$Pd(OAc)_2$	P(*t*Bu$_2$).BiPh	LiCl	DME	50
7	$Pd_2(dba)_3$	P(fur)$_3$	LiCl	DME	50
8	$Pd_2(dba)_3$	P(*t*Bu$_3$).HBF_4	LiCl	DME	50
9	$Pd_2(dba)_3$	dppe	LiCl	DME	50
10	$Pd(OAc)_2$	dppe	LiCl	MeCN	50
11	$Pd(OAc)_2$	P(fur)$_3$	LiCl	MeCN	50

Reactions were carried out on a 0.21 mmol scale with 3 equiv. CsF and 0.6 equiv. LiCl in 1 mL solvent.

Despite screening a variety of reaction conditions, using a range of different ligands, palladium sources and solvents none of the three component coupling product was generated. The main product identified was unreacted benzyl bromide with small amounts of aniline present in some cases. Despite purifying several of the reactions by HPLC not even small quantities of 3CC could be isolated. Again, a more

comprehensive screen of reaction conditions, in particular solvent and temperature, may yield more promising results.

4.4 An alternative approach – σ-bond insertion

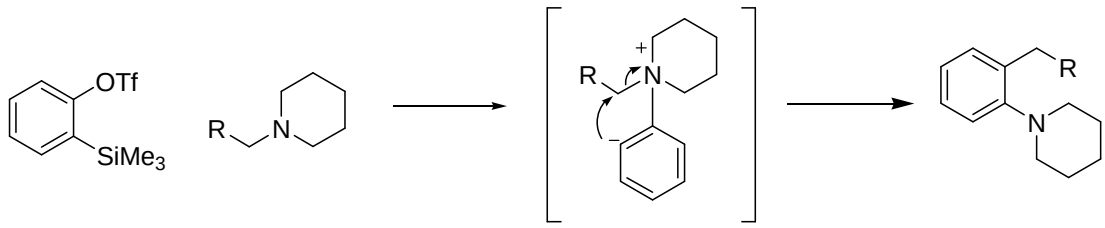


Figure 4.6 Proposed C-N σ-bond insertion

As the three component Buchwald reaction has been unsuccessful, an alternative approach to generating 1,2-disubstituted aromatics through formation of a C-C and C-N bond was sought. A route that has particular potential is σ-bond insertion, where a tertiary amine might nucleophilically attack benzyne, the aryl anion generated then reacting with an electrophilic carbon centre, which subsequently breaks one of the amine's C-N bonds (Figure 4.6). A similar reaction involving migration of a methyl group has been previously reported; treatment of N,N-dimethylaniline **246** with pentafluorophenyl lithium **245** generated the 1,2-substituted product **248** in a yield of 19% (Figure 4.7).[186] The authors postulate, however, that this occurs via an inter- rather than intra-molecular process.

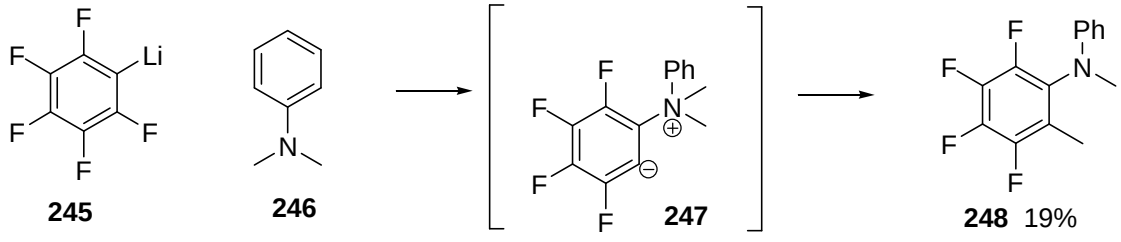


Figure 4.7 Benzyne insertion into a C-N σ-bond

Recent publications in this area lend precedence to this idea, with the work of Stoltz and Yoshida, who demonstrated that benzyne can be inserted into the α,β-carbon-

carbon bond of β-ketoesters and 1,3-diketones, bearing the most similarity (Figure 1.44).[84, 85] One significant difference in the present investigation is that previously reported σ-bond insertions which require cleavage of a carbon bond have all utilised a ketone group, or ketone equivalent, as the electrophilic portion of the molecule (Figure 1.45).

Initial studies focussed on the use of benzyl amines, with the intention being that the benzylic carbon would prove to be a suitably electrophilic site. Utilising either DME or MeCN at either room temperature or 50 ºC, none of the desired product was isolated. Where starting materials were not recovered unchanged, the main product was *N*-phenylpiperidine which is presumably produced from initial quaternisation with benzyne followed by loss of the benzyl group. It is perhaps not surprising that a successful reaction could not be observed; the four membered ring transition state that would form is disfavoured by Baldwin's rules, being a 4-endo-tet ring closure and the worst-case scenario in terms of orbital overlap. A more suitable system was therefore sought.

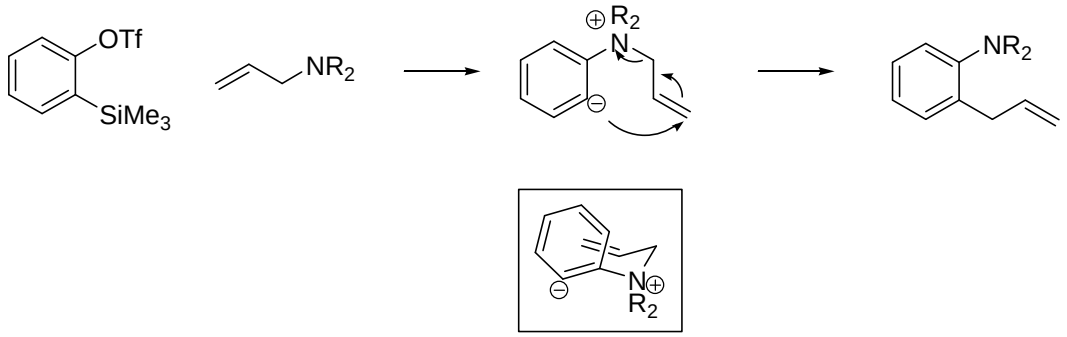


Figure 4.8 Aza-Claisen type reaction with allyl amines

Allyl amines could constitute a system that would adopt a more favourable 6-membered cyclic transition state. The aryl anion generated in this case could potentially attack the terminal carbon of the allyl chain, the double bond migrating followed by C-N bond cleavage in a process reminiscent of an aza-Claisen type reaction. This 3,3 sigmatropic rearrangement has been reported to work well with electron deficient alkynes such as dimethyl acetylenedicarboxylate (DMAD)[187]

(Figure 4.8) but an analogous reaction with benzyne has not been successfully described. Subsequent to his successful optimisation of the aza-Claisen reaction with DMAD, Kandeel sought to replace the alkyne with benzyne, generated from decomposition of benzenediazonium-2-carboxylate, however did not observe any of the aza-Claisen product.[187]

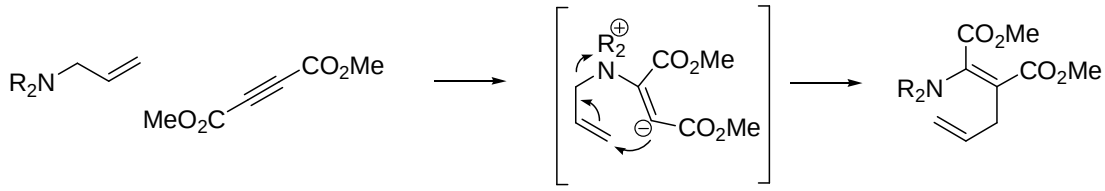
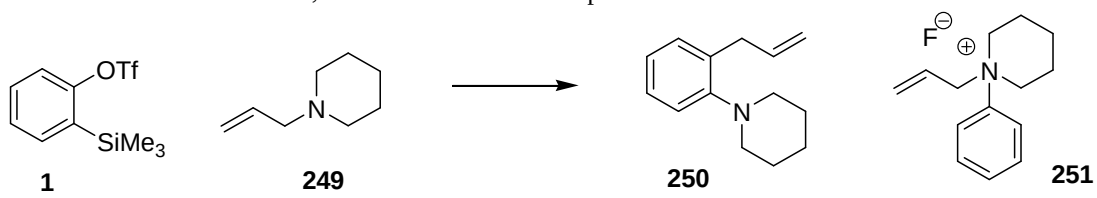


Figure 4.9 Aza-Claisen reaction with DMAD

The aza-Claisen reaction generally occurs at elevated temperatures, in comparison to a standard Claisen reaction, often requiring 250 – 300 ºC and being particularly prone to the formation of undesired by-products.[188] Reaction temperature can be lowered significantly by employing acid catalysis, Lewis acids proving particularly efficient.[189] In terms of the reaction of amines with DMAD, utilising either protic or Lewis acid catalysts can lower reaction temperature such that reactions can proceed at room temperature or below.[190]

Table 4.4 Screen of solvents, fluoride sources and temperature



1 **249** **250** **251**

Entry	Fluoride Source	Solvent (Ratio)	Temp	Yield (250)
1	CsF	MeCN	rt	0%
2[a]	KF	MeCN	rt	0%
3[a]	KF	THF	rt	0%
4[a]	KF	THF	65 ºC	0%
5	CsF	MeCN	65 ºC	0%
6	CsF	THF	65 ºC	0%[b]
7	CsF	DME	65 ºC	0%
8	CsF	MeCN	85 ºC	0%[b]
9	CsF	THF/Toluene (1:1)	85 ºC	0%[b]
10	CsF	DME	85 ºC	0%[b]

Reactions were carried out on a 0.2 mmol scale with a 1:1 ratio of benzyne:allyl amine and 3 equiv. fluoride source. [a] 1 equiv. 18-crown-6 added. [b] Trace product identified by crude NMR and TLC but not isolated.

Initial reactions utilised allyl piperidine **249**, with temperature, fluoride source and solvent being the variables examined. At lower temperatures in a variety of solvents none of the Claisen product was obtained (Table 4.4). Instead the quaternary salt **251** resulting from nucleophilic addition of the tertiary amine to benzyne followed by protic quench was isolated. Thus it could be clearly seen that benzyne will successfully quaternise the tertiary amine, however the aza-Claisen requires more forcing conditions, with trace amounts being observed as the reaction temperature was increased. The anion may be quenched either by abstracting a proton from solvent, from water perhaps present in the CsF or during work-up. By changing to acetonitrile/toluene mixtures and increasing the reaction temperature to >100 ºC it was possible to obtain the aza-Claisen product **250**. Reducing the solvent volume

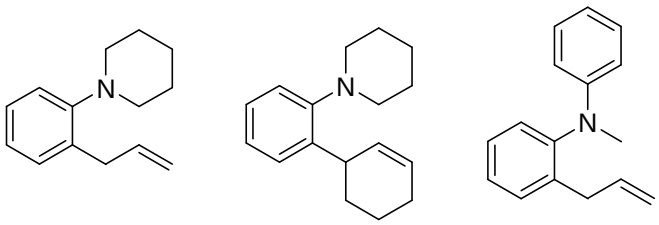
and increasing the reaction time further improved the yield of **250** to 92% (Table 4.5).

Table 4.5 Optimisation studies for benzyne aza-Claisen

Entry	Time (h)	Ratio Toluene/MeCN	Volume (mL/mmol)	Yield (250)
1	12	9:1	1.7	0%
2	24	1:1	0.7	25%
3	24	3:1	0.7	36%
4	48	1:1	0.5	85%
5	48	3:1	0.5	76%
6	48	4:1	0.5	52%
7[a]	48	3:1	0.5	90%
8	48	3:1	1	75%
9	48	3:1	0.25	92%

Reactions were carried out on a 0.3 mmol scale with 1.5 equiv. allyl amine and 3 equiv. CsF at reflux.
[a] 1.5 equiv. benzyne precursor with 0.3 mmol amine was used.

A limited number of transition metal Lewis acid catalysts were also screened in the reaction, none giving a successful result. At either room temperature or 65 ºC, 5 mol% $AuCl_3$, AgOTf or $Pd(OAc)_2$ failed to promote the reaction. At room temperature the quaternary salt **251** was isolated, however at 65 ºC the allyl group eliminated, leaving phenyl piperidine as the sole product.



250 92% **252** 71% **253** 91%

Figure 4.10 Benzyne aza-Claisen reaction has been successful for a small number of tertiary allyl amines.

Utilising the conditions as in Entry 9, Table 4.5, a limited selection of allyl amines have been examined (Figure 4.10). High yields can be obtained using both aromatic and allylic tertiary allyl amines. Electron rich aryne precursors such as 3,6-dimethyl, 3-methoxy (**258**) and naphthyl (**167**) also take part in the reaction, with only slightly attenuated yields.[191, 192]

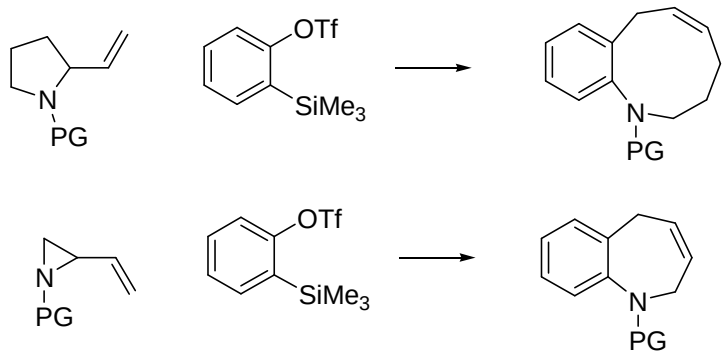


Figure 4.11 Ring opening would yield interesting heterocycles

Further examination of this reaction is, of course, required. A wider range of aliphatic and aromatic amines should be utilised to illustrate the reaction scope. Employing heterocyclic allylamines such as *N*-allyl indole and allyl amides would demonstrate the nucleophilic requirements for reactivity, whilst substituted arynes would show the steric and electronic factors that affect nucleophilic addition. Some interesting heterocyclic systems could potentially be formed by employing 2-vinyl cyclic amines such as 2-vinylpyrrolidine (Figure 4.11).[192]

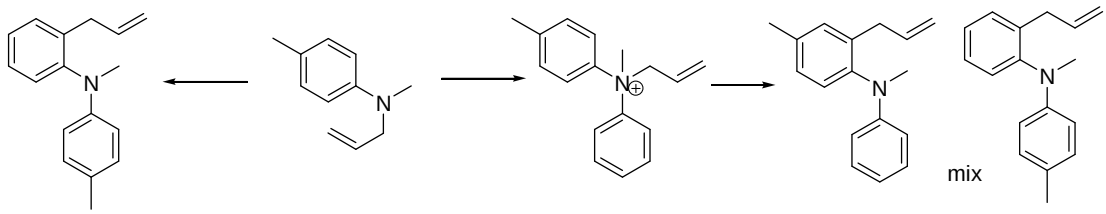


Figure 4.12 Substituted aniline would show if reaction occurs *via* a concerted or two-step process

Mechanistically, substituted anilines could be used to prove if the reaction is concerted or if the arylanion is undergoing a protic quench followed by thermal Claisen reaction of the quaternary amine intermediate (Figure 4.12). As high

temperatures and long reaction times are necessary for the Claisen reaction to occur, it is most likely that the latter pathway is in operation. A second mechanistic consideration is whether the reaction is proceeding via a six-membered transition state, in an aza-Claisen type process, as would be predicted, or if a four-membered transition state is forming. Utilising allyl amines containing substituents on the allyl group should give conclusive proof of the mechanistic pathway; if the allyl group contains a terminal substituent, for example, this will be transposed to the position closest to benzene if an aza-Claisen mechanism is in action, remaining at the terminal position if a more straightforward σ-bond insertion occurs (Figure 4.13).

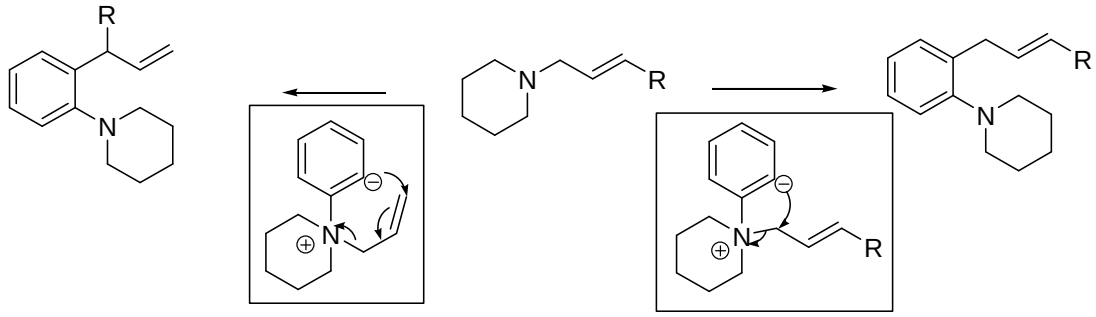


Figure 4.13 Allylic substitution will show whether the reaction proceeds via a 4- or 6- membered transition state.

The benzyne aza-Claisen reaction of allyl amines has the potential to be a very powerful method for the formation of interesting 1,2-substituted aromatic and bicyclic compounds. However, a significant amount of research is clearly required both in developing the methodology and investigating the full range of substrates that can be used.

5 Conclusions and Future Work

A positive start has been made in the search for palladium catalysed three component couplings, although the application of benzyne as a third component in the full range of palladium catalysed couplings has not been realised. The aims of the project were to demonstrate that carbopalladation of benzyne was feasible and that the aryl palladium species generated could be successfully reacted with a second component, and this has been achieved. The range of electrophiles that can be used in couplings has been expanded from allyl chlorides, the only electrophile reported at the outset of the project, to α-bromo esters, benzyl bromides and aryl iodides. These have been applied, with arynes, in the Heck reaction, generating a wide range of structural diversity in a single operation and in good yield. Developed conditions have then been applied to the synthesis of pharmacologically interesting target molecules, making significant improvements over previously published syntheses. Mechanistically, inroads have been made into elucidating the order of incorporation, with certain potential reaction pathways being conclusively discarded. Although firm conclusions about the mechanism have not yet been made, the reaction being more complex than was initially postulated, the evidence gathered thus far should assist in future studies.

Although other three component coupling reactions have not yet been successfully developed, initial investigations have been promising, paving the way for future advancements in a range of other couplings. In particular, the Buchwald reaction to form a C-C and C-N bond proved unsuccessful after some lengthy optimisation, the problem of nucleophilic attack of amines towards benzyne being tough to overcome. In order to progress towards such structures an alternative benzyne reaction is being developed, forming the bonds firstly by nucleophilic attack of a tertiary amine on benzyne, followed by electrocyclic rearrangement to yield the desired 1,2-substituted arenes. Further development of this reaction should find an efficient method for the synthesis of both mono- and bicyclic compounds.

5.1 Future work – palladium couplings

Much work remains to be done in this field, the area of transition metal catalysed aryne chemistry being still in its infancy. As mentioned above, successful conditions for the use of arynes in the Heck reaction with a range of electrophiles has been developed, however these conditions have not proved to be entirely general. Future investigations in this area should focus on the use of the remaining electrophiles, namely alkyl and vinyl halides and acid chlorides. Expansion of the procedures to incorporate the use of aryl and heteroaryl chlorides and bromides would also significantly expand the utility of the process. It would also be worth examining other alkenes that have so far failed to yield successful reactions.

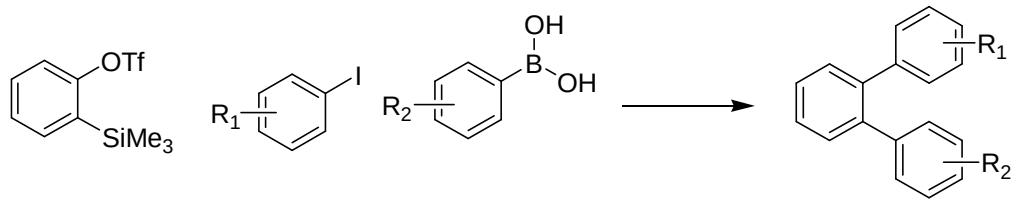


Figure 5.1 Proposed three component Suzuki reaction

Although both the Stille and Suzuki reactions have been reported with allyl chlorides, further work on these reactions with the full range of electrophiles would allow for the generation of an even wider range of structural diversity; in particular the Suzuki reaction with aryl iodides would allow for the formation of interesting triaryl compounds (Figure 5.1), whilst the Stille reaction is often employed in the synthesis of natural products, organotin compounds being tolerant of a wide range of functionality. Initial scoping of the Suzuki reaction of an aryl iodide, benzyne and an aryl boronic acid produced a 15% yield of the triaryl 3CC product, demonstrating that these couplings are achievable.

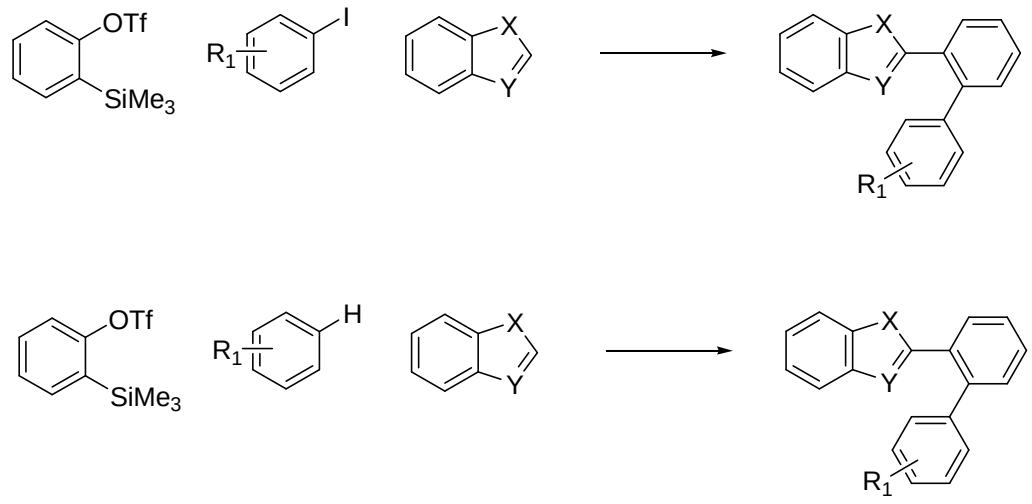


Figure 5.2 Direct arylation incorporating benzyne

Further, development of heteroaromatic C-H insertion reactions would prove to be a highly interesting and impressive reaction, forming complex and interesting molecular structures without the requirement for a pre-functionalised heteroaromatic (Figure 5.2). Although development of conditions for this reaction is fraught with difficulty, those commonly employed for C-H activation being incompatible with the use of arynes, the rapid rate of publications forthcoming in this area is likely to present findings that will point the way. Were a successful coupling to be found, a procedure for the reaction of an unsubstituted aromatic, by electrophilic aromatic substitution, followed by incorporation of the aryne and then a heteroaromatic would form the same structural types without the requirement for a halide. If palladium catalysed methodology for such a transformation continues to be elusive alternate strategies could be pursued; potentially the heteroaryl anion could be used to nucleophilically attack benzyne, the aryl anion then having the potential to be trapped with an external electrophile or be protically quenched (Figure 5.3). Such a reaction would generate 2-aryl heteroaromatics without the requirement for transition metals, affording a useful methodology.

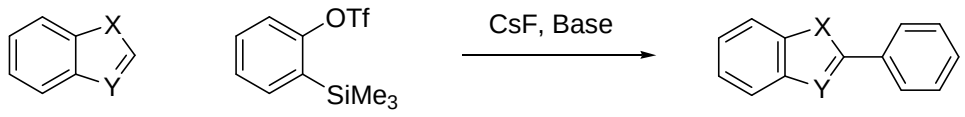


Figure 5.3 Transition metal free direct arylation of heterocycles

As advances in cross-coupling reactions progress to the use of alternative metals, as has already been demonstrated in some areas with the use of copper in the Buchwald reaction and nickel in Negishi couplings, an opportunity to expand the use of benzyne in synthesis presents itself. As well as studying the interactions of benzyne with a range of metals, cross-couplings using a range of catalysts should allow for careful control of the products formed, perhaps yielding alternative outcomes for the same substrates depending on the metal employed.

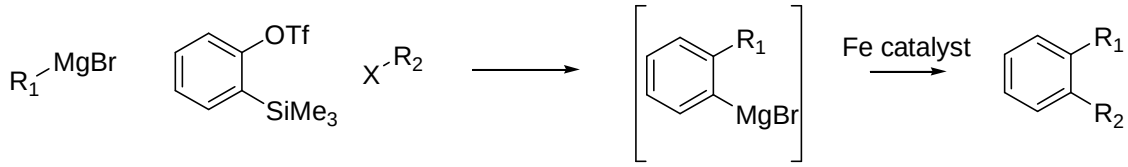


Figure 5.4 Tandem nucleophilic Grignard addition and Fuerstner iron-catalysed coupling

An alternative to metal catalysed three-component couplings would be to use arynes in a tandem process where one stage of the reaction is catalysed by a metal. For example, Fuerstner's powerful iron-catalysed chemistry could potentially be combined with aryne chemistry. By making suitable use of the inherent electrophilicity of arynes in their reaction with magnesium reagents a carbon-carbon or carbon-heteroatom bond could be formed along with an aryl-magnesium bond. This species would then take part in a rapid iron-catalysed reaction with an organohalide, overall producing a three component coupling with the formation of two bonds (Figure 5.4). It would be expected that suitable selectivity could be achieved providing that the initial magnesium species selected is significantly less reactive in the iron catalysed process than the aryl magnesium that is generated.

Iron-catalysed reactions are reported to occur rapidly, thus reaction of the intermediate with a second aryne should also be avoidable. A similar process for the Kumada-Corriu reaction could also be proposed, however as this reaction is significantly slower than the iron-catalysed chemistry selectivity may be harder to achieve.

5.2 Future work – aryne chemistry

In the area of aryne chemistry much work remains before arynes are commonly looked to as a robust method in a wide range of synthetic techniques. In particular, a broader range of aryne precursors, containing a wider range of functionalities as well as heteroaromatic derivatives of these, needs to be reported, and their generation rates and reactivities in a range of reactions fully developed. In terms of their generation and reactivity, little work has been reported as to examining the effects of different substituents on the rates of aryne generation, the sensitivities of the arynes and their reaction rates. Consideration of these factors, which are probably best assessed by NMR studies, should lead to more facile adjustment of reaction conditions to achieve maximum yields from a wide range of substrates. Such a study would hopefully provide insight into why some aryne precursors have been ineffective in palladium couplings.

A straightforward method for the synthesis of these precursors that is both robust and that can be carried out on scale is also necessary. Application of solid supported synthesis techniques to aryne chemistry would also prove to be a worthwhile area for future research, eliminating problems with two component coupling or the formation of multi-benzyne components.

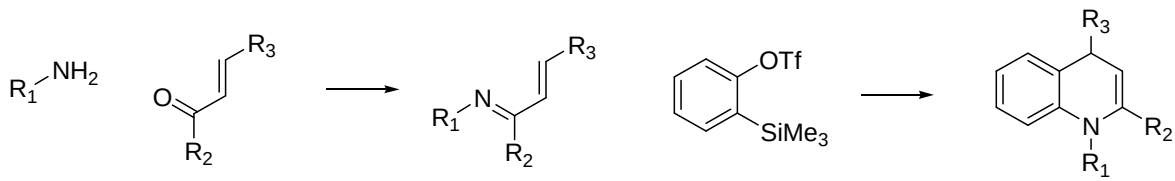


Figure 5.5 Possible aza-Diels-Alder reaction

Along with palladium couplings there are still areas in both nucleophilic additions and pericyclic reactions that merit further study. For example, although aryne Diels-Alder reactions are well reported, little work has been done on aza-Diels-Alder reactions. This is probably due to many of the reported reactions being inverse electron demand Diels-Alder reactions, to which arynes are not suited. For example, condensation of α,β-unsaturated ketones with an amine, followed by reaction with arynes to give 1,4-dihydroquinolines would be a powerful method of forming the heterocyclic structure, the possibility of encorporating a chiral auxiliary to influence the stereochemical outcome could further enhance the usefulness of such a procedure (Figure 5.5). There also remains a huge number of nucleophilic addition reactions to be investigated. In particular the possibility of incorporating external electrophiles allows for a range of structural diversity to be incorporated, along with the further development of σ-bond insertions.

6 Experimental

6.1 General Techniques

^{1}H nuclear magnetic resonance (NMR) spectra were recorded at ambient temperature on either a Brüker AC250 (250 MHz), Brüker DPX360 (360 MHz) or Brüker DPX400 (400 MHz) instrument and calibrated to residual solvent peaks ($CDCl_3$ 7.26 ppm or DMSO 2.50 ppm). The data is presented as follows: chemical shift (in ppm on the δ scale), integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), assignment and the coupling constant (J, in Hertz). The ^{13}C NMR spectra were recorded using an internal deuterium lock for the indicated reference at ambient probe temperatures on Brüker AC250 (63 MHz), Brüker DPX360 (91 MHz) or Brüker DPX400 (100.5 MHz) instrument and calibrated to residual solvent peaks ($CDCl_3$ 77.0 ppm or DMSO 39.4 ppm). They are reported in ppm on the δ scale followed by the interpretation determined from the Distorsionless Enhancement Polarisation

Transfer (DEPT) spectra and multiplicity (as above). ^{19}F NMR spectra were recorded at ambient temperature on a Brüker AC250 (235 MHz) or Brüker DPX400 (377 MHz) instrument. The data is reported as chemical shift in ppm on the δ scale, multiplicity and coupling constant (J, in Hertz).

IR spectra were recorded on a JASCO FT/**IR**-460 plus instrument using 4 mm sodium chloride disks. The wavelengths of the maximum absorbance (ν_{max}) are quoted in cm^{-1}. Electrospray high resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using a Finnigan MAT 900 XLT double focusing mass spectrometer, at University of Edinburgh using a Thermo MAT 900 double focusing mass spectrometer or at Organon Laboratories using an Applied Biosystems Mariner Time Of Flight mass spectrometer. The data is recorded as the ionisation method followed by the calculated and measured masses. Elemental analysis was performed using a Carlo Erba CHNS analyser at the University of St Andrews. Melting points were determined on a Gallenkamp Electrothermal melting point apparatus and are uncorrected.

TLC was performed on Merck 60F254 silica plates and visualised by UV light and/or anisaldehyde or potassium permanganate stains. The compounds were purified by

wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure or using a Biotage or Biotage SP4 with pre-packed 12M columns. The eluent is quoted as a percentage. Solvents were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com or purchased (anhydrous) from Aldrich unless otherwise stated. DME was distilled over sodium with benzophenone as an indicator or purchased anhydrous from Aldrich. Starting materials and catalysts were purchased from a chemical supplier and used as received unless otherwise stated. 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate was kindly provided by Andrew Stretton.

6.2 Experimental Procedures and Data

6.2.1 Some Comments on the Synthesis of Aryne Precursors

Before beginning work on palladium catalysed couplings using arynes, preparation of suitable precursors was required. Although the unsubstituted benzyne precursor is commercially available, other aryne and heteroaryne precursors required synthesis. As mentioned previously, the synthesis first reported by Kobayashi involved 3 steps from *o*-bromophenol (Figure 6.1). This has since been modified by Guitian and co-workers to a two-step procedure where the second stage involves a retro-Brook rearrangement, silicon migrating from oxygen to carbon, followed by formation of the triflate (Figure 6.2). It was found, however, that this procedure can be somewhat unreliable particularly in the case of precursors containing electron donating groups, leading to cleavage of the carbon-silicon bond. There is also the potential problem of the substrate, once formed, undergoing a base promoted anionic thia-Fries rearrangement, leading to a di-*ortho* substituted phenol which could then react with a second triflate or undergo a Brook rearrangement, cleaving the carbon-silicon bond.[45] Thus a longer but more efficient procedure was developed for substrates where the literature procedure was found to be ineffectual.

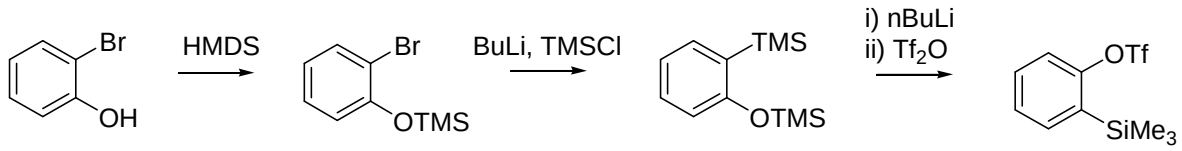


Figure 6.1 Kobayashi's original synthesis

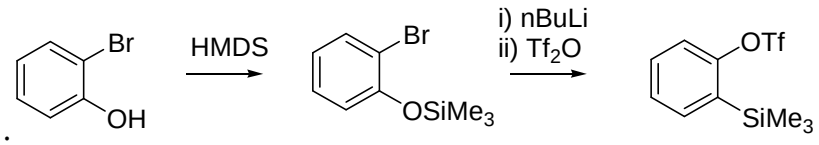


Figure 6.2 Shorter protocol reported by Guitian

Where the respective 2-bromophenols were not commercially available two tactics were employed. In some cases it is possible to selectively brominate *ortho* to the phenol group, and this was used to make the sesamol derivative. Directed lithiation could be employed where a methoxy substituent *ortho* to the benzyne triple bond was desired. However, it was found that during the triflation step cleavage of the carbon-silicon bond was a major problem, yielding the unsubstituted triflate as the major product. Even using mild pyridine-triflic anhydride conditions that are frequently employed in the literature, a significant amount of desilylation was observed. This issue could be circumvented by deprotecting the TMS-ether using mild conditions, K_2CO_3 in organic solvent, followed by triflation using N-phenyltrifluoromethanesulfonimide (Figure 6.3).

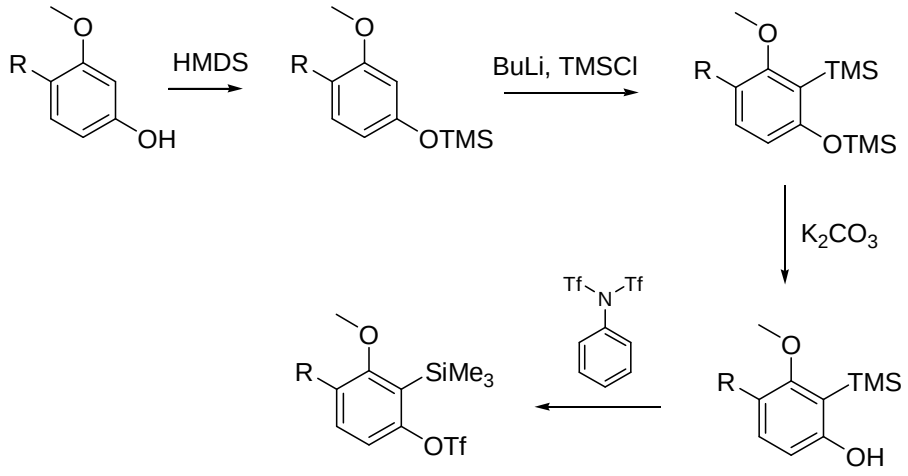


Figure 6.3 Synthesis of electron rich aryne precursors utilising an *ortho*-lithiation and mild triflation.

For the hetarynes, both 2,3- and 3,4- pyridine precursors have been reported, although in both cases only one of the two possible silyl-triflate regioisomers. The 2,3-pyridyne precursor was prepared using the procedures of Shay in two steps from 2-hydroxypyridine (Figure 6.4).[37]

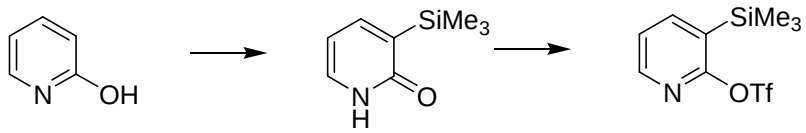
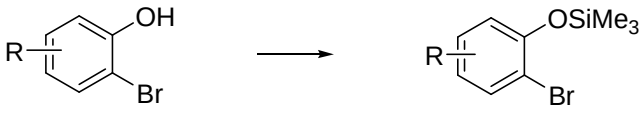


Figure 6.4 Synthesis of 2,3-pyridyne precursor

6.2.2 Synthesis of aryne precursors

6.2.2.1 Preparation of phenoxytrimethylsilanes

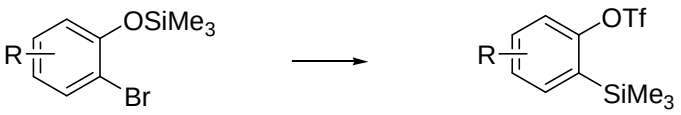


Procedure A: A mixture of phenol (1 equiv.) and hexamethyldisilazane (0.6 equiv.) was stirred at 80 °C for 45 mins. Excess HMDS and ammonia were removed under vacuum.

Procedure B: A mixture of phenol (1 equiv) and hexamethyldisilazane (0.6 equiv.) in THF was stirred at reflux for 90 mins. Solvent, excess HMDS and ammonia were removed under vacuum.[56]

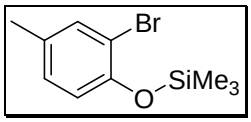
Products were of sufficient purity to use in subsequent reactions.

6.2.2.2 General procedure for conversion of 2-bromophenoxy silanes to triflate benzyne precursors.



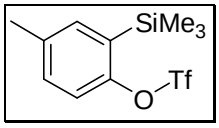
To a solution of 2-bromophenoxy silane (1 equiv.) in THF (0.15 M) cooled to -100 °C (liquid N_2/Et_2O) n-butyl lithium (1.1 equiv.) was added dropwise and the reaction

stirred for 20 mins whilst being allowed to warm to -80 °C. The reaction was cooled again to -100 °C, followed by the dropwise addition of triflic anhydride (1.2 equiv). After a further 20 mins cold, saturated $NaHCO_3$ was added, the phases separated and the aqueous layer extracted with three portions of ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Products were purified by chromatography on silica gel using MPLC, eluting with DCM/hexanes.[56]



(2-Bromo-4-methylphenoxy)trimethylsilane

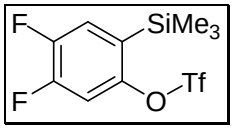
From 2-bromo-4-methyl phenol using procedure A. Isolated as a colourless oil in quantitative yield. **^{1}H NMR** ($CDCl_3$, 250 MHz) δ 7.35 (dd, 1H, Ar*H*, J = 2.1, 0.7 Hz), 6.99 (m, 1H, Ar*H*), 6.77 (d, 1H, Ar*H*, J = 8.2 Hz), 2.28 (s, 3H, ArCH_3), 0.30 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 149.7 (quat), 133.2 (CH), 132.0 (quat), 128.5 (CH), 120.0 (CH), 114.7 (quat), 19.9 (CH_3), 0.0 (CH_3).



4-Methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate 254[106]

Isolated as a colourless oil in a yield of 62%. **^{1}H NMR** ($CDCl_3$, 250 MHz) δ 7.31 (m, 1H, Ar*H*), 7.22 (s, 2H, Ar*H*), 2.37 (s, 3H, ArCH_3), 0.35 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** (CDCl3, 63 MHz) δ 153.1 (quat), 137.2 (quat) 136.7 (CH), 132.2 (quat), 131.7 (CH), 119.3 (CH), 20.8 (CH_3), -0.8 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -75.2 (s).

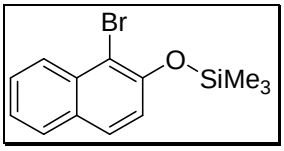
The spectroscopic data was in agreement with that previously published.



4,5-Difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate 165[57]

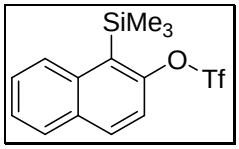
From 2-bromo-4,5-difluorophenol using procedure A. Isolated as a colourless oil in a yield of 78%. **^{1}H NMR** ($CDCl_3$, 250 MHz) δ 7.31 (d, 1H, Ar*H*, J = 9.2 Hz), 7.22 (dd, 1H, Ar*H*, J = 9.1, 4.1 Hz), 0.32 (s, 9H, Si(CH_3)$_3$); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -75.1, -132.2 (d, J_{FF} = 20.6 Hz), -139.5 (d, J_{FF} = 20.6 Hz).

The spectroscopic data was in agreement with that previously published



(1-Bromonaphthalen-2-yloxy)trimethylsilane

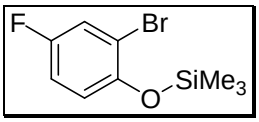
From 1-bromonaphthalen-2-ol using procedure B. Isolated as a colourless oil in quantitative yield. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 8.28 (d, 1H, Ar*H*, J = 8.5 Hz), 7.82 (d, 1H, Ar*H*, J = 8.1 Hz), 7.75 (d, 1H, Ar*H*, J = 8.8 Hz), 7.60 (dt, 1H, Ar*H*, J = 8.3, 1.2 Hz), 7.45 (dt, 1H, Ar*H*, J = 8.0, 1.0 Hz), 7.17 (d, 1H, Ar*H*, J = 8.8 Hz), 0.40 (s, 9H, $Si(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 150.6 (quat), 133.4 (quat), 130.3 (quat), 128.6 (CH), 128.0 (CH), 127.5 (CH), 126.5 (CH), 124.5 (CH), 121.4 (CH), 112.5 (quat), 0.6 (3C, CH_3).



1-(Trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate 167[104]

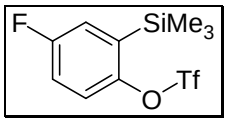
Isolated as a colourless oil in a yield of 68%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 8.22 (m, 1H, Ar*H*), 7.93 – 7.89 (m, 2H, Ar*H*), 7.59 – 7.55 (m, 2H, Ar*H*), 7.42 (d, 1H, Ar*H*, J = 9.0 Hz), 0.60 (s, 9H, $Si(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 90 MHz) δ 152.5 (quat), 137.6 (quat), 132.5 (CH), 132.4 (quat), 129.3 (quat), 129.0 (CH), 128.8 (CH), 126.8 (CH), 126.3 (CH), 119.2 (CH), 118.7 (CF_3, q, J = 320.7 Hz), 2.2 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -74.1 (s).

The spectroscopic data was in agreement with that previously published.



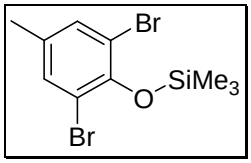
(2-Bromo-4-fluorophenoxy)trimethylsilane

From 2-bromo-4-fluorophenol using procedure B. Isolated as a colourless oil in quantitative yield. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.30 (dd, 1H, Ar*H*, J_{HH} = 3.0 Hz, J_{HF} = 7.9 Hz), 6.95 (ddd, 1H, Ar*H*, J_{HH} = 8.9, 3.0 Hz, J_{HF} = 7.7 Hz), 6.85 (dd, 1H, Ar*H*, J_{HH} = 8.9 Hz, J_{HF} = 5.1 Hz), 0.32 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 157.0 (CF, d, J = 243.4 Hz), 148.9 (quat, d, J = 2.8 Hz), 120.8 (CH, d, J = 8.5 Hz), 120.0 (CH, d, J = 25.6 Hz), 115.3 (quat, d, J = 10.1 Hz), 114.9 (CH, d, J = 22.6 Hz), 0.3 (3C, CH_3).



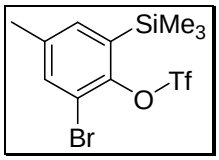
4-Fluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate 164[193]

Isolated as a colourless oil in a yield of 76%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.31 (dd, 1H, Ar*H*, J_{HH} = 9.0, J_{HF} = 4.0), 7.20 (dd, 1H, Ar*H*, J_{HH} = 3.2, J_{HF} = 8.1), 7.11 (ddd, 1H, Ar*H*, J_{HH} = 9.0, 3.2, J_{HF} = 7.3), 0.37 (s, 9H, Si(C*H*$_3$)$_3$) ; **^{13}C NMR** ($CDCl_3$, 90 MHz) δ 161.0 (CF, d, J = 250.1 Hz), 150.2 (quat, d, J = 2.6 Hz), 135.9 (quat, d, J = 4.6 Hz), 122.4 (CH, d, J = 21.8 Hz), 121.5 (CH, dd, J = 8.0, 1.5 Hz), 118.5 (CF_3, q, J = 320.0 Hz), 117.7 (CH, d, J = 24.3 Hz), -1.0 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ –75.2 (s), -115.8 (s).



(2,6-Dibromo-4-methylphenoxy)trimethylsilane

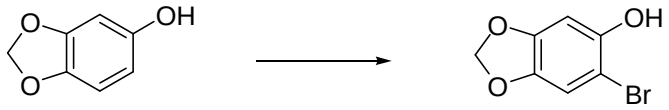
From 2,6-dibromo-4-methylphenol using procedure B. Isolated as a colourless oil in quantitative yield. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.32 (s, 2H, Ar*H*), 2.29 (s, 3H, ArCH_3), 0.40 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 148.4 (quat), 133.4 (quat), 132.8 (2C, CH), 115.7 (2C, quat), 20.0 (CH_3), 1.4 (3C, CH_3).



2-Bromo-4-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate 168[56]

Isolated as a colourless oily solid in a yield of 35%. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48 (s, 1H, Ar*H*), 7.26 (s, 1H, Ar*H*), 2.35 (s, 3H, ArCH_3), 0.39 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 146.7 (quat), 139.3 (quat), 137.0 (quat), 136.2 (CH), 136.1 (CH), 118.6 (CF_3, q, J = 318.8 Hz), 116.0 (quat), 20.5 (CH_3), 0.0 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ –72.9.

The spectroscopic data was in agreement with that previously published.

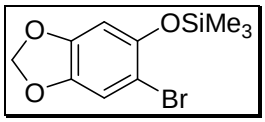


6-Bromobenzo[d][1,3]dioxol-5-ol[194]

Bromine (20.71 mmol, 1.061 ml, 3.31 g) in acetic acid (4.5 ml) was added dropwise to a suspension of benzo[d][1,3]dioxol-5-ol (26.4 mmol, 3.64 g) in acetic acid (8 ml) at 0 °C. After addition the crimson reaction was poured onto ice and the resulting greenish solid isolated by filtration. The product was dried in a vac oven at 25°C. Isolated as a greenish solid in a yield of 2.85g, 50%.[194] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.89 (s, 1H, Ar*H*), 6.59 (s, 1H, Ar*H*), 5.93 (s, 2H, CH_2), 5.19 (s, 1H, O*H*); **^{13}C**

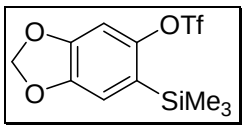
NMR (CDCl3, 101 MHz) δ 147.4 (quat), 142.0 (quat), 110.6 (CH), 101.7 (CH_2), 99.2 (quat), 98.1 (CH).

The spectroscopic data was in agreement with that previously published.



(6-Bromobenzo[d][1,3]dioxol-5-yloxy)trimethylsilane

From 6-Bromobenzo[d][1,3]dioxol-5-ol using procedure B. Isolated as a dark green oil in quantitative yield. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.94 (s, 1H, Ar*H*), 6.43 (s, 1H, Ar*H*) 5.91 (s, 2H, CH_2), 0.27 (s, 9H, Si(CH_3)$_3$).

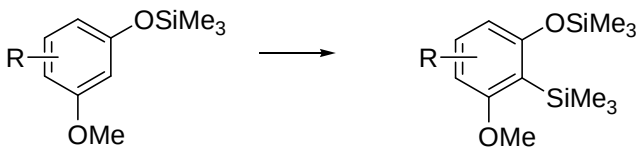


6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate 255[110]

Isolated as a colourless oil in a yield of 35%. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.88 (s, 1H, Ar*H*), 6.85 (s, 1H, Ar*H*), 6.03 (s, 2H, CH_2), 0.34 (s, 9H, SiCH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 149.5 (quat), 148.7 (quat), 146.9 (quat), 124.9 (quat), 118.5 (CF_3, q, J = 320.0 Hz), 113.2 (CH), 102.4 (CH_2), 102.3 (CH), -0.7 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –73.9 (s).

The spectroscopic data was in agreement with that previously published.

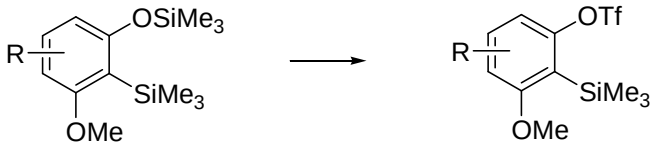
6.2.2.3 General procedure for conversion of 3-substituted phenoxysilanes to (siloxyphenyl)trimethylsilanes.



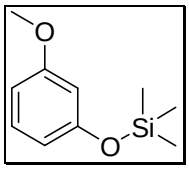
A solution of (phenoxy)trimethylsilane (1 equiv.) in THF (15 mL) was added dropwise to a solution of LDA in THF (8 mL), freshly prepared from

diisopropylamine (1.2 equiv.) and nBuLi (1.1 equiv.), at -78 °C. The resulting solution was stirred at room temperature for 90 mins then cooled again to -78 °C. TMSCl (1.2 equiv.) was added and the reaction allowed to reach room temp and stirred overnight. Sat. NH_4Cl was added and the reaction extracted with 3 × ether. Combined organics were dried over Na_2SO_4, filtered and concentrated. Products were purified using MPLC, eluting with DCM/hexane.[57]

6.2.2.4 General procedure for conversion of (siloxyphenyl)trimethylsilanes to triflates.

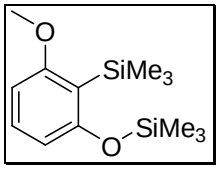


(Siloxyphenyl)trimethylsilane was taken up in EtOAc/MeOH (10:1) and K_2CO_3 (1 equiv.) was added. The reaction was stirred at room temperature until all starting materials had been consumed, then water added. The phases were separated and the aqueous washed with 3 × EtOAc. Combined organics were dried over Na_2SO_4, filtered and concentrated. The crude reaction was dissolved in DMF and to this added Cs_2CO_3 (1 equiv.) and N-phenyltrifluoromethanesulfonimide (1 equiv.). The reaction was stirred for 30 mins then quenched with $NaHCO_3$. The reation was extracted with 3 × EtOAc, combined organics washed with brine then dried over Na_2SO_4, filtered and concentrated. Purification by silica gel chromatography (DCM/Hexanes) yielded the title compounds.



(3-Methoxyphenoxy)trimethylsilane

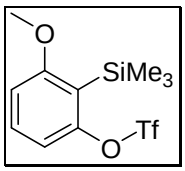
From 3-methoxyphenol using procedure A. Isolated as a colourless oil in quantitative yield. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.14 (t, 1H, Ar*H*, J = 8.0 Hz), 6.55 (ddd, 1H, Ar*H*, J = 8.3, 2.4, 0.7 Hz), 6.47 (m, Ar*H*, 1H), 6.42 (t, 1H, Ar*H*, J = 2.4 Hz), 3.79 (s, 3H, OCH_3), 0.28 (s, 9H, Si(CH_3)$_3$).



(2-Methoxy-6-trimethylsiloxyphenyl)trimethylsilane[57]

From (3-methoxyphenoxy)trimethylsilane. Product isolated as a colourless oil in a yield 67%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.19 (t, 1H, Ar*H*, J = 8.1 Hz), 6.48 (d, 1H, Ar*H*, J = 8.2 Hz), 6.44 (dd, 1H, J = 8.1, 0.7 Hz), 3.76 (s, 3H, OCH_3), 0.34 (s, 9H, Si(CH_3)$_3$), 0.30 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 90 MHz) δ 165.8 (quat), 161.2 (quat), 130.9 (CH), 116.7 (quat), 110.8 (CH), 103.3 (CH), 55.1 (CH_3), 1.5 (3C, CH_3), 0.8 (3C, CH_3).

The spectroscopic data was in agreement with that previously published

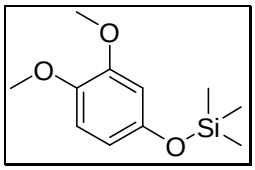


3-Methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate 256[57]

Isolated as a colourless oil in a yield of 45%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.37 (t, 1H, Ar*H*, J = 8.3 Hz), 6.95 (d, 1H, Ar*H*, J = 8.4), 6.84 (d, 1H, Ar*H*, J = 8.3 Hz), 3.83 (s, 3H, OCH_3), 0.37 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** (CDCl3, 90 MHz) δ 165.5 (quat), 154.7 (quat), 131.6 (CH), 120.8 (quat), 118.6 (CF_3, q, J = 320.8), 113.3 (CH), 112.7

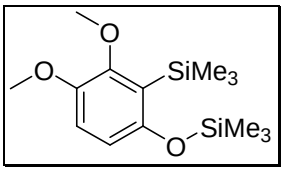
(CH), 109.5 (CH), 55.6 (CH_3), 0.75 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ –74.0.

The spectroscopic data was in agreement with that previously published



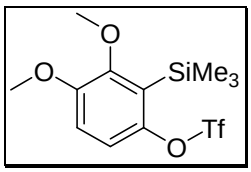
(3,4-Dimethoxyphenoxy)trimethylsilane

From 3,4-dimethoxyphenol using procedure B. Isolated as a colourless oil in quantitative yield. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 6.76 (d, 1H, Ar*H*, J = 8.6 Hz), 6.47 (d, 1H, Ar*H*, J = 2.7 Hz), 6.40 (dd, 1H, Ar*H*, J = 8.6, 2.7 Hz), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 0.28 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 149.6 (quat), 149.3 (quat), 143.9 (quat), 111.8 (CH), 110.5 (CH), 105.0 (CH), 56.3 (CH_3), 55.8 (CH_3), 0.5 (3C, CH_3).



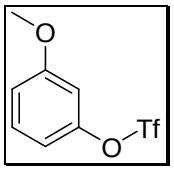
(2,3-Dimethoxy-6-trimethylsiloxyphenyl)trimethylsilane

Product isolated as a colourless oil in a yield of 69%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 6.81 (d, 1H, Ar*H*, J = 8.7 Hz), 6.50 (d, 1H, Ar*H*, J = 8.7 Hz), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 0.35 (s, 9H, Si(CH_3)$_3$), 0.33 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 154.7 (quat), 154.2 (quat), 146.9 (quat), 123.3 (quat), 114.5 (CH), 112.2 (CH), 60.8 (CH_3), 56.2 (CH_3), 1.4 (3C, CH_3), 0.7 (3C, CH_3).



3,4-Dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate 257[195]

From 3,4-dimethoxy-2-(trimethylsilyl)phenol (**16**). Isolated as a colourless oil in a yield of 71%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.04 (d, 1H, Ar*H*, J = 8.6 Hz), 6.92 (d, 1H, Ar*H*, J = 8.6 Hz), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 0.39 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 90 MHz) δ 154.3 (quat), 151.6 (quat), 147.9 (quat), 126.6 (quat), 118.6 (CF_3, q, J = 320.8 Hz), 116.0 (CH), 113.7 (CH), 60.9 (CH_3), 55.9 (CH_3), 1.0 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -74.2.

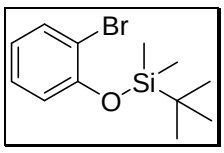


3-Methoxyphenyl trifluoromethanesulfonate[196]

Isolated as a colourless oil in a yield of 72% from attempts to convert (2-Methoxy-6-trimethylsiloxyphenyl)trimethylsilane to 3-methoxy-2-(trimethylsilyl)phenyltrifluoro methanesulfonate using butyl lithium and triflic anhydride as described by Peña *et. al.*[57]

^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.36 (t, 1H, Ar*H*, J = 8.3 Hz), 6.95 – 6.87 (m, 2H, Ar*H*), 6.82 (t, 1H, Ar*H*, J = 2.4 Hz), 3.85 (s, 3H, OCH_3); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 160.9 (quat), 150.25 (quat), 130.6 (CH), 118.7 (CF_3, q, J = 320.8 Hz), 114.1 (CH), 113.2 (CH), 107.5 (CH), 55.7 (CH_3); **^{19}F NMR** ($CDCl_3$, 235.3 MHz) δ – 74.2.

The spectroscopic data was in agreement with that previously published.

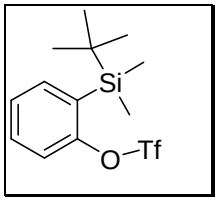


(2-Bromophenoxy)(tert-butyl)dimethylsilane 258[56]

To a stirred solution of 2-bromophenol (1.05 mL, 9 mmol) and imidazole (1.150 g, 16.9 mmol) in DCM (50 mL) was added *tert*-butyldimethylsilyl chloride (2.45 g, 16.2 mmol) and the reaction stirred at room temperature for 2 hours. Water (50 mL) was added and the phases separated, the aqueous phase being extracted with DCM (2 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and

concentrated yielding the title compound as a colourless oil (2.60 g, 100%). **^{1}H NMR** ($CDCl_3$, 250 MHz) δ 7.61 (dd, 1H, Ar*H*, J = 7.9, 1.7 Hz), 7.28 (m, 1H, Ar*H*), 6.98 (m, 2H, Ar*H*), 1.16 (s, 9H, $C(CH_3)_3$), 0.36 (s, 6H, $Si(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 151.5 (quat), 132.3 (CH), 127.1 (CH), 121.2 (CH), 119.1 (CH), 114.2 (quat), 24.6 (2C, CH_3), 17.2 (3C, CH_3).

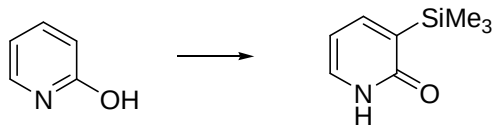
The spectroscopic data was in agreement with that previously published



2-(*tert*-butyldimethylsilyl)phenyl trifluoromethanesulfonate 116[56]

(2-bromophenoxy)(tert-butyl)dimethylsilane **258** (2.59 g, 9 mmol) was dissolved in THF (30 mL) and the solution cooled to -80 °C (dry ice/Et_2O). *n*-Butyl lithium (4.16 mL, 2.47 M, 9.9 mmol) was added dropwise and the reaction stirred for 20 mins. This was followed by the dropwise addition of triflic anhydride (1.9 mL, 11.25 mmol). After a further 20 mins cold, saturated $NaHCO_3$ (30 mL) was added, the phases separated and the aqueous layer extracted with ether (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated yielding the title compound as a colourless oil, 1.85 g, 60.3%. **^{1}H NMR** ($CDCl_3$, 250 MHz) δ 7.56 (dd, 1H, Ar*H*, J = 7.6, 1.8 Hz), 7.53 - 7.33 (m, 3H, Ar*H*), 0.89 (s, 9H $C(CH_3)_3$), 0.40 (s, 6H, $Si(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 156.0 (quat), 137.9 (CH) 131.5 (CH), 129.9 (quat), 127.2 (CH), 119.3 (CF_3), 26.9 (3C, CH_3), 17.9 (quat), -4.3 (2C, CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -75.2 (s).

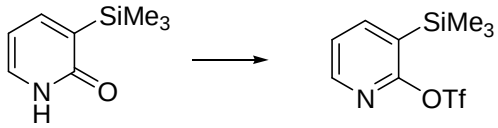
The spectroscopic data was in agreement with that previously published.



3-Trimethylsilyl-2-hydroxypyridine 259[37]

A solution of LDA was prepared by adding *n*-BuLi (14.8 mL, 1.6M) to a solution of diisopropylamine (3.30 mL) in ether (43 mL) which was cooled in an ice bath then allowed to warm to rt. The LDA solution was added dropwise to 2-hydroxypyridine (1.02g) and the heterogeneous mixture was stirred. After 30 mins TMSCl (3.15 mL) was added to the slurry and allowed to stir overnight. The mixture was filtered and the solvent removed to leave a yellow/brown oil. The mixture was stirred overnight in EtOAc/silica to eliminate any disilylated material, leaving a brown solid after filtration and concentration. Crude NMR suggested some of the disilylated product remained so the mixture was stirred with silica for a second overnight then filtered and concentrated to yield 1.43 g, 80% of a yellow oil. Crude product was deemed to be of sufficient purity to use for the subsequent step.

^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.54 (dd, 1H, Ar*H*, J = 2.2, 6.5 Hz), 7.35 (dd, 1H, Ar*H*, J = 2.2, 6.4 Hz), 6.23 (t, 1H, Ar*H*, J = 6.5 Hz), 0.27 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 167.7 (quat), 147.3 (CH), 135.5 (CH), 131.5 (quat), 106.5 (CH), -1.8 (CH_3).



3-(Trimethylsilyl)pyridin-2-yl trifluoromethanesulfonate 166[37]

To a solution of 3-trimethylsilyl-2-hydroxypyridine **259** (738 mg, 4.41 mmol) and 2,6-di-tertbutyl-4-methylpyridine (1.0 g, 4.87 mmol) in DCM (20 mL) was added dropwise triflic anhydride (0.82 mL, 4.87 mmol). A precipitate formed as the mixture was stirred for 1 hour. Solvent was removed in vacuo and the residue washed with hexane. Combined organics were concentrated, product being isolated

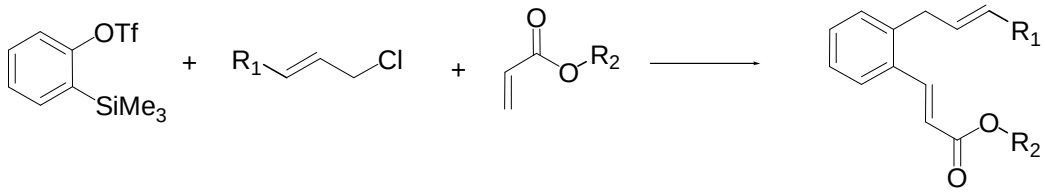
after chromatography on silica eluting with 5% EtOAc/hexane as a colourless oil, 1.23 g, 93%.

^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.32 (dd, 1H, Ar*H*, J = 2.1, 4.8 Hz), 7.92 (dd, 1H, Ar*H*, J = 2.1, 7.2 Hz), 7.31 (dd, 1H, Ar*H*, J = 4.8, 7.2 Hz), 0.37 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 160.7 (quat), 148.6 (CH), 146.8 (CH), 125.0 (quat), 123.1 (CH), 118.3 (CF_3, q, J = 320.5 Hz), -1.7 (CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -74.2 (s).

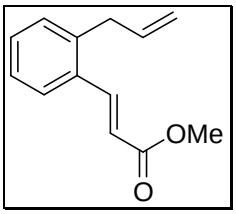
The spectroscopic data was in agreement with that previously published.

6.3 Heck Reactions

6.3.1 3CC of benzyne, allyl chloride and methyl acrylate

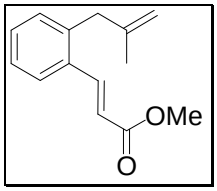


Acrylate (0.49 mmol, 2.4 equiv.) and allyl chloride (0.25 mmol, 1.2 equiv.) were added to a stirred suspension of $Pd(OAc)_2$ (2 mg, 5 mol %), dppe (4 mg, 5 mol %) and CsF (4 equiv.) in freshly distilled DME (1.5 mL) under N_2 in a 5 mL round bottomed flask. This was followed by the dropwise addition of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate (**1**) (0.21 mmol, 1 equiv.). The reaction was heated to 50 ºC and stirred overnight. The reaction mixture was diluted with DCM and filtered through a short plug of silica then concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with 10% EtOAc/hexanes yielded the title compounds.



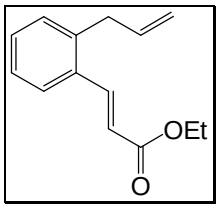
(*E*)-methyl 3-(2-allylphenyl)acrylate 89

Isolated as a colourless oil in a yield of 50%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 8.06 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.58 (dd, 1H, Ar*H*, J = 7.5, 1.4 Hz), 7.33 (dd, 1H, Ar*H*, J = 7.2, 1.4 Hz), 7.32 – 7.25 (m, Ar*H*, 2H), 6.37 (d, 1H, CH=C*H*, J = 15.8 Hz), 5.96 (m, $CH_2C\mathit{H}=CH_2$, 1H), 5.08 (dd, 1H, CH=CH_2, J = 10.1, 1.6 Hz), 5.00 (dd, 1H, CH=CH_2, J = 15.3, 1.7 Hz), 3.83 (s, OCH_3, 3H), 3.58 (d, 2H, CH_2CH, J = 7.7 Hz); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 167.4 (quat), 142.4 (CH), 139.2 (quat), 136.5 (CH), 133.3 (quat), 130.3 (CH), 130.2 (CH), 126.8 (CH), 126.6 (CH), 119.1 (CH), 116.4 (CH_2), 51.7 (CH_3), 37.4 (CH_2); **IR** (film/cm^{-1}) 2949, 1717, 1634, 1434, 1318, 1272, 1194, 1171; **HRMS** (ES^+) cald. for $C_{13}H_{15}O_2$: $(M+H)^+$ 203.1067; Found 203.1067.



(E)-methyl 3-(2-(2-methylallyl)phenyl)acrylate 91

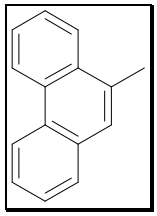
Isolated as a colourless oil in a yield of 36%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 8.18 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.77 (m, 1H, Ar*H*), 7.45 - 7.6 (m, 3H, Ar*H*), 6.56 (d, 1H, CH=C*H*, J = 15.8 Hz), 5.05 (s, 1H, C=CH_2), 4.72 (s, 1H, C=CH_2), 4.00 (s, 3H, OCH_3), 3.59 (s, 2H, CH_2), 2.04 (s, 3H, CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 167.9 (quat), 144.7 (quat), 143.0 (CH), 139.5 (quat), 134.1 (quat), 131.3 (CH), 130.4 (CH), 127.2 (CH), 126.9 (CH), 119.3 (CH), 112.9 (CH_2), 52.1 (CH_3), 41.9 (CH_2), 23.1 (CH_3); **IR** (film/cm^{-1}) 2950, 1717, 1632, 1433, 1320, 1275; **HRMS** (ES^+) cald. for $C_{14}H_{16}O_2$: $(M+H)^+$ 216.1145; Found 216.1145.



(E)-ethyl 3-(2-allylphenyl)acrylate 92[197]

Isolated as a colourless oil in a yield of 41%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 8.06 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.62 (dd, 1H, Ar*H*, J = 7.6, 1.4 Hz), 7.36 (dd, 1H, Ar*H*, J = 7.4, 1.4 Hz), 7.29 (m, 2H, Ar*H*), 6.40 (d, 1H, CH=C*H*, J = 15.8 Hz), 6.00 (m, 1H, C*H*=CH_2), 5.13 (dd, 1H, CH=CH_2, J = 10.1, 1.6 Hz), 5.04 (dd, 1H, CH=CH_2, J = 17.1, 1.7 Hz), 4.31 (q, 2H, CH_2CH$_3$, J = 3.7 Hz), 3.57 (d, 2H, ArCH_2, J = 7.7 Hz), 1.39 (t, 3H, CH_2CH_3, J = 5.4 Hz); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 167.4 (quat), 142.5 (CH), 139.6 (quat), 136.9 (CH), 133.8 (quat), 130.6 (CH), 130.5 (CH), 127.2 (CH), 127.0 (CH), 120.0 (CH), 116.8 (CH_2), 60.9 (CH_2), 37.9 (CH_2), 14.7 (CH_3).

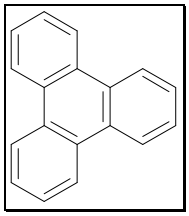
The spectroscopic data was in agreement with that previously published.



9-Methylphenanthrene 90[198]

Isolated as a colourless solid as a by-product. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.66 (m, 1H, Ar*H*), 8.59 (m, 1H, Ar*H*), 7.99 (m, 1H, Ar*H*), 7.72 (m, 1H, Ar*H*), 7.61-7.57 (m, 2H, Ar*H*), 7.53-7.49 (m, 3H, Ar*H*) 2.67 (s, 3H, CH_3).

The spectroscopic data was in agreement with that previously published.

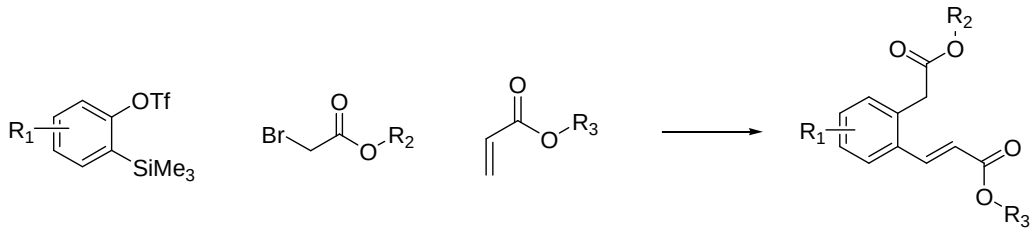


Triphenylene 48[199]

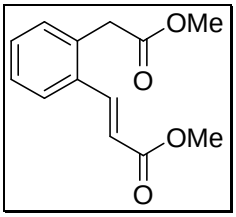
Isolated as colourless needles as a by-product. **m.p** 185 - 187 ^{o}C; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.60 (m, 6H, Ar*H*), 7.59 (m, 6H, Ar*H*). **^{13}C NMR** (63 MHz, $CDCl_3$) δ 129.7, 127.1, 123.2.

The spectroscopic data was in agreement with that previously published.

6.3.2 General method for TCC of benzyne, bromoacetates and acrylates

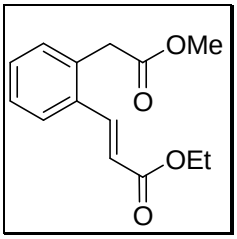


Methyl acrylate (0.31 mmol, 1.5 equiv.) and methyl bromoacetate (0.21 mmol, 1 equiv.) were added to a stirred suspension of $Pd(dppf)Cl_2$ (8.4 mg, 5 mol%) and CsF (4.5 equiv.) in freshly distilled DME (1 ml) under N_2. This was followed by the dropwise addition of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate (**1**) (0.31 mmol, 1.5 equiv.). The reaction was stirred at 50 ºC over two nights, after which time it was diluted with DCM and filtered through a short plug of silica then concentrated under reduced pressure. Flash chromatography on silica gel, eluting with 20% EtOAc/hexanes yielded the title compounds.



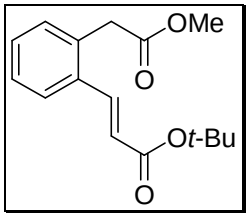
(*E*)-methyl 3-(2-((methoxycarbonyl)methyl)phenyl)acrylate 108

Isolated as a colourless oil in a yield of 75%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.96 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.60 (dd, 1H, Ar*H*, J = 1.6, 7.3 Hz), 7.38 - 7.27 (m, Ar*H*, 3H), 6.38 (d, 1H, CH=C*H*, J = 15.8 Hz), 3.81 (s, OCH_3, 3H), 3.81 (s, ArCH_2, 2H), 3.70 (s, OCH_3, 3H); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 171.3 (quat), 167.1 (quat), 141.8 (CH), 133.9 (quat), 133.5 (quat), 131.1 (CH), 130.1 (CH), 127.9 (CH), 126.9 (CH), 120.0 (CH), 52.2 (CH_3), 51.7 (CH_3), 38.6 (CH_2); **IR** (film/cm^{-1}) 2952, 1716, 1634, 1434, 1319, 1170; **HRMS** (ES^+) cald. for $C_{13}H_{15}O_4$: $(M+H)^+$ 235.0965. Found: 235.0967.



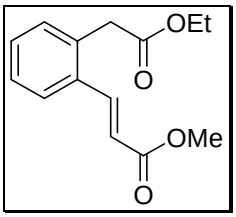
(E)-ethyl 3-(2-((methoxycarbonyl)methyl)phenyl)acrylate 117

Isolated as a colourless oil in a yield of 65%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.86 (d, 1H, CH=C*H*, J = 15.7 Hz), 7.50 (m, 1H, Ar*H*), 7.27 - 7.16 (m, 3H, Ar*H*), 6.29 (d, 1H, CH=C*H*, J = 15.7 Hz), 4.18 (q, 2H, CH_2CH$_3$, J = 7.1 Hz), 3.62 (s, 2H, CH_2), 3.60 (s, 3H, OCH_3), 1.25 (t, 3H, CH$_2$CH_3, J = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 171.3 (quat), 166.7 (quat), 141.5 (CH), 134.0 (quat), 133.5 (quat), 131.0 (CH), 130.1 (CH), 127.8 (CH), 126.9 (CH), 120.5 (CH), 60.5 (CH_2), 52.2 (CH_3), 38.5 (CH_2), 14.3 (CH_3); **IR** (film/cm^{-1}) 2970, 1720, 1634, 1434, 1322, 1201; **HRMS** (ES^+) cald. for $C_{14}H_{16}O_4$: $(M+H)^+$ 248.1044; Found 248.1043.



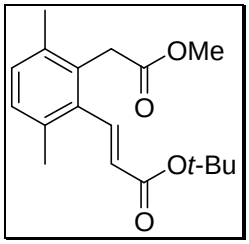
(*E*)-tert-butyl 3-(2-((methoxycarbonyl)methyl)phenyl)acrylate 118

Isolated as a colourless oil in a yield of 80%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.86 (d, 1H, CH=C*H*, J = 15.7 Hz), 7.59 (m, 1H, Ar*H*), 7.37 - 7.25 (m, 3H, Ar*H*), 6.31 (d, 2H, CH=C*H*, J = 15.7 Hz), 3.78 (s, 2H, ArCH_2), 3.70 (s, 3H, OCH_3), 1.52 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 171.3 (quat), 165.9 (quat), 140.3 (CH), 134.0 (quat), 133.2 (quat), 130.8 (CH), 129.7 (CH), 127.6 (CH), 126.7 (CH), 122.2 (CH), 80.4 (quat), 52.0 (CH_3), 38.4 (CH_2), 28.0 (3C, CH_3); **IR** (film/cm^{-1}) 2978, 1740, 1708, 1633, 1321, 1151; **HRMS** (ES^+) cald. for $C_{16}H_{21}O_4$: $(M+H)^+$ 277.1434. Found: 277.1435.



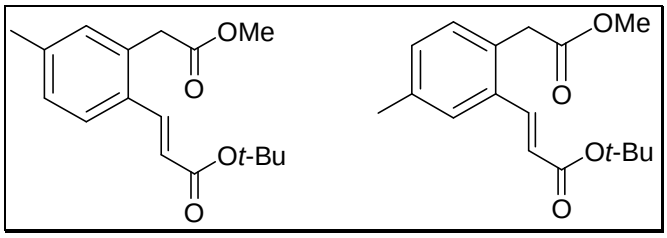
(*E*)-methyl 3-(2-((ethoxycarbonyl)methyl)phenyl)acrylate 119

Isolated as a colourless oil in a yield of 59%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.98 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.60 (dd, 1H, Ar*H*, J = 1.6, 7.3 Hz), 7.38 - 7.27 (m, 3H, Ar*H*), 6.36 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.15 (q, 2H, CH_2CH$_3$ J = 7.1 Hz), 3.83 (s, 3H, CH_3), 3.77 (s, 2H, ArCH_2), 1.25 (t, 3H, CH$_2$CH_3, J = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 171.3 (quat), 167.6 (quat), 142.4 (CH), 134.3 (quat), 134.1 (quat), 131.5 (CH), 130.5 (CH), 128.2 (CH), 127.3 (CH), 120.3 (CH), 61.5 (CH_2), 52.1 (CH_3), 39.3 (CH_2), 14.5 (CH_3); **IR** (film/cm^{-1}) 2970, 1718, 1633, 1440, 1315, 1153; **HRMS** (ES^+) cald. for $C_{14}H_{16}O_4$: $(M+H)^+$ 248.1044. Found: 248.1043.



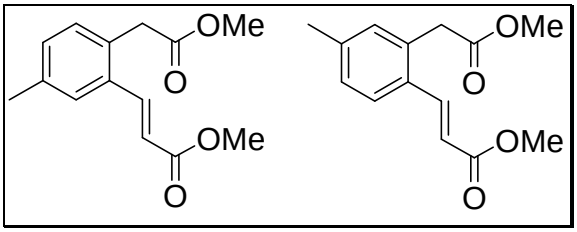
(E)-*tert*-butyl 3-(2-((methoxycarbonyl)methyl)-3,6-dimethylphenyl)acrylate 120

Isolated as a colourless oil in a yield of 59%. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.71 (d, 1H, CH=C*H*, J = 16.4 Hz), 7.05 (s, 2H, Ar*H*), 5.89 (d, 1H, CH=C*H*, J = 16.4 Hz), 3.70 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 2.27 (s, 6H, 2 × ArCH_3), 1.54 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.8 (quat), 165.7 (quat), 144.7 (CH), 135.8 (quat), 135.0 (quat), 133.9 (quat), 130.8 (quat), 130.0 (CH), 129.1 (CH), 126.9 (CH), 80.6 (quat), 52.0 (CH_3), 36.2 (CH_2), 28.2 (3 × CH_3), 20.8 (CH_3), 19.9 (CH_3); **IR** (film/cm^{-1}) 2977, 1740, 1712, 1641, 1435, 1368, 1314, 1248; **HRMS** (ES^+) cald for $C_{16}H_{21}O_4$: $(M+H)^+$ 304.16691. Found: 304.16746.



(*E*)-*tert*-butyl 3-(2-((methoxycarbonyl)methyl)-4-methylphenyl)acrylate and (*E*)-*tert*-butyl 3-(2-((methoxycarbonyl)methyl)-5-methylphenyl)acrylate 121

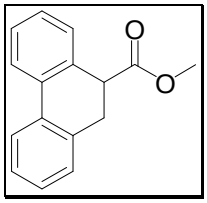
Isolated as a colourless oil in a yield of 70%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.75 (d, 1H, CH=C*H*, J = 15.7 Hz), 7.42 (d, 0.5H, Ar*H*, J = 7.9 Hz), 7.34 (s, 0.5H , Ar*H*), 7.07 (m, 3H, Ar*H*), 6.22 (d, 0.5H, CH=C*H*, J = 15.7 Hz), 6.20 (d, 0.5H, CH=C*H*, J = 15.7 Hz), 3.66 (s, 1H, ArCH_2), 3.64 (s, 1H, ArCH_2), 3.63 (s, 1.5H, OCH_3), 3.61 (s, 1.5H, OCH_3), 2.27 (s, 3H, CH_3), 1.44 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 171.6 (quat), 171.6 (quat), 166.2 (quat), 166.1 (quat), 140.6 (CH), 140.3 (CH), 140.2 (quat), 137.4 (quat), 133.8 (quat), 133.3 (quat), 131.7 (CH), 131.2 (quat), 130.9 (CH), 130.7 (CH), 130.5 (quat), 128.6 (CH), 127.4 (CH), 126.7 (CH), 122.0 (CH), 121.2 (CH), 80.5 (quat), 80.4 (quat), 52.2 (CH_3), 52.1 (CH_3), 38.5 (CH_2), 38.1 (CH_2), 28.1 (CH_3), 21.2 (CH_3), 21.0 (CH_3); **IR** (film/cm^{-1}) 2978, 1741, 1707, 1633, 1321, 1251, 1151; **HRMS** (ES^+) cald for $C_{13}H_{13}O_3$: $(M\text{-}O^tBu)^+$ 217.0859. Found: 217.0852.



(E)-methyl 3-(2-((methoxycarbonyl)methyl)-5-methylphenyl) and (E)-methyl 3-(2-((methoxycarbonyl)methyl)-4-methylphenyl)acrylate 122

Isolated as a colourless oil in a yield of 52%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.93 (d, 1H, CH=C*H*, J = 15.7 Hz), 7.52 (d, 0.5H, Ar*H*, J = 7.9 Hz), 7.41 (s, 0.5H, Ar*H*), 7.19 (s, 1H, Ar*H*), 7.17 (d, 0.5H, Ar*H*, J = 7.9 Hz), 7.09 (s, 0.5H, Ar*H*), 6.37 (2 × d, 1H, CH=C*H*, J = 15.7 Hz), 3.81 (s, 1.5H, OCH_3), 3.80 (s, 1.5H, OCH_3), 3.76 (s, 1H, CH_2), 3.75 (s, 1H, CH_2), 3.70 (s, 1.5H, OCH_3), 3.69 (s, 1.5H, OCH_3), 2.4 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 63 MHz) δ 171.9 (quat), 167.7 (quat), 142.4 (CH), 142.1

(CH), 140.9 (CH), 137.9 (CH), 134.1 (quat), 133.1 (quat), 132.2 (CH), 131.4 (CH), 129.1 (quat), 127.8 (CH), 127.2 (CH), 120.1 (CH), 119.3 (CH), 52.5 (CH_3), 52.0 (CH_3), 38.9 (CH_2), 38.6 (CH_2), 21.6 (CH_3), 21.4 (CH_3); **IR** (film/cm^{-1}) 2971, 1707, 1633, 1313, 1250, 1198; **HRMS** Calcd $C_{14}H_{16}O_4$ (M + NH_4) 266.1387; Found (M + NH_4) 266.1389.

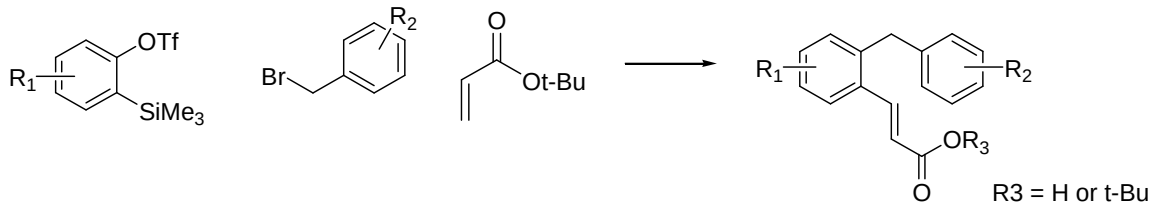


Methyl 9,10-dihydrophenanthrene-9-carboxylate 109a[200]

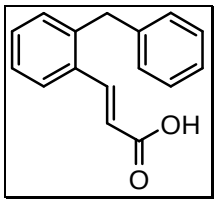
Isolated as a colourless oil as a by-product. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.87 (t, 2H, Ar*H*), 7.45 (m, 2H, Ar*H*), 7.35 (m, 4H, Ar*H*), 4.00 (t, 1H, C*H*, J = 5.8 Hz), 3.72 (s, 3H, OCH_3), 3.32 (dd, 2H, CH_2, J = 5.8, 1.8 Hz); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 173.4 (quat), 134.4 (quat), 134.0 (quat), 133.6 (quat), 133.5 (quat), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 124.0 (CH), 123.6 (CH), 52.0 (CH_3), 44.5 (CH), 31.6 (CH_2).

The spectroscopic data was in agreement with that previously published.

6.3.3 General method for 3CC of benzyl bromides, benzyne and acrylates



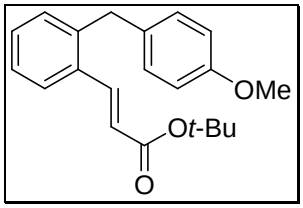
Benzyl bromide (0.31 mmol, 1.5 equiv.) and *tert*-butyl acrylate (0.21 mmol, 1 equiv.) were added to a stirred suspension of $Pd(OAc)_2$ (2.4 mg, 5 mol %), dppe (4.3 mg, 5 mol %) and CsF (3 equiv) in freshly distilled DME (1 ml) under N_2. This was followed by the dropwise addition of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate (**1**) (0.21 mmol, 1 equiv.). The reaction was stirred at 50 ºC over 2 nights. The reaction mixture was diluted with DCM and filtered through a pad of silica. Purification was achieved either by a) chromatography on silica gel eluting with EtOAc/hexanes to produce the ester, or b) treatment with TFA (0.3 mL) in DCM (1 mL) at room temperature followed by concentration under reduced pressure to afford a residue which could be triturated and / or recrystallised from hexane/EtOAc mixtures to afford the crystalline acids.



(*E*)-3-(2-benzylphenyl)acrylic acid 130

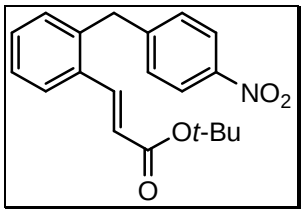
Isolated in 65% yield as a colourless solid. **m.p.** (hexanes) 126 - 128 ºC; **^{1}H NMR** (DMSO, 360 MHz) δ 7.89 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.77 (d, 1H, Ar*H*, J = 7.6 Hz), 7.43 - 7.34 (m, 5H, Ar*H*), 7.19 (m, 1H, Ar*H*), 7.11 (d, 2H, Ar*H*, J = 7.3 Hz) 6.41 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.15 (s, 2H, ArCH_2); **^{13}C NMR** (DMSO, 91 MHz) δ 166.9 (quat), 140.7 (quat), 139.9 (CH), 139.5 (CH), 132.4 (quat), 130.4 (CH), 129.7 (quat), 128.0 (CH), 127.8 (CH), 126.5 (CH), 126.3 (CH), 125.5 (CH), 119.8 (CH),

37.6 (CH_2); **IR** (film/cm^{-1}) 1684, 1624, 1418, 1283, 1220; **HRMS** (ES^-) cald for $C_{16}H_{13}O_2$: $(M-H)^-$ 237.0910. Found: 237.0911.



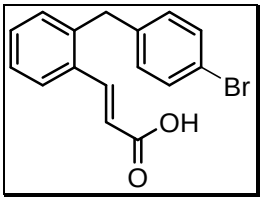
(*E*)-tert-butyl 3-(2-(4-methoxybenzyl)phenyl)acrylate 132

Isolated in a 76% yield as a colourless oil; **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.98 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.62 (dd, 1H, Ar*H*, J = 7.4, 1.1 Hz), 7.45 - 7.22 (m, 3H, Ar*H*), 7.11 (d, 2H, Ar*H*, J = 8.6 Hz), 6.87 (d, 2H, Ar*H*, J = 8.6 Hz), 6.30 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.12 (s, 2H, ArCH_2), 3.82 (s, 3H, OCH_3), 1.58 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 165.9 (quat), 157.7 (quat), 140.9 (quat), 140.2 (CH), 133.4 (quat), 132.0 (quat), 130.2 (CH), 129.6(CH), 129.4 (CH), 126.5 (CH), 126.4 (CH), 121.4 (CH), 113.6 (CH) 80.1 (quat), 54.9 (CH_3), 37.9 (CH_2), 27.9 (CH_3); **IR** (film/cm^{-1}) 2977, 1707, 1511, 1320, 1248, 1150; **HRMS** (ES^+) cald for $C_{21}H_{25}O_3$: $(M+H)^+$ 325.1798. Found: 325.1802.



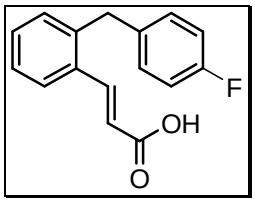
(*E*)-tert-butyl 3-(2-(4-nitrobenzyl)phenyl)acrylate 133

Isolated in 69% yield as a colourless oil; **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 8.17 (d, 2H, Ar*H*, J = 8.4 Hz), 7.82 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.63 (dd, 1H, Ar*H*, J = 7.4, 1.4 Hz), 7.42 - 7.34 (m, 2H, Ar*H*), 7.32 (d, 2H, Ar*H*, J = 8.4 Hz), 7.23 (dd, 1H, Ar*H*, J = 7.4, 1.4 Hz), 6.29 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.26 (s, 2H, ArCH_2), 1.50 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 165.7 (quat), 147.8 (quat), 146.2 (quat), 140.1 (CH), 137.8 (quat), 133.6 (quat), 130.6 (CH), 129.9 (CH), 129.2 (CH), 127.4 (CH), 126.8 (CH), 123.6 (CH), 122.1 (CH), 80.5 (quat), 38.7 (CH_2), 27.9 (CH_3); **IR** (film/cm^{-1}) 2977, 1707, 1519, 1346, 1151; **HRMS** (ES^+) cald for $C_{16}H_{12}NO_3$: $(M-O^tBu)^+$ 266.0812. Found: 266.0815.



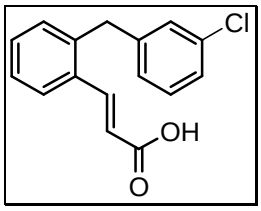
(*E*)-3-(2-(4-bromobenzyl)phenyl)acrylic acid 134

Isolated in a yield of 80% as a light yellow solid. **m.p.** (hexanes) 174 ºC; **^{1}H NMR** (DMSO, 360 MHz) δ 7.99 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.69 (d, 1H, Ar*H*, J = 6.4, 1.4 Hz), 7.48 (d, 2H, Ar*H*, J = 8.3 Hz), 7.43 - 7.31 (m, 3H, Ar*H*), 7.08 (d, 2H, Ar*H*, J = 8.3 Hz), 6.41 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.14 (s, 2H, ArCH_2); **^{13}C NMR** (DMSO, 91 MHz) δ 167.3 (quat), 141.0 (CH), 139.9 (quat), 139.4 (quat), 132.9 (quat), 131.3 (CH), 130.9 (CH), 130.6 (CH), 130.2 (CH), 127.2 (CH), 126.9 (CH), 120.6 (CH), 119.1 (CH), 37.4 (CH_2); **IR** (film/cm^{-1}) 1685, 1627, 1486, 1418, 1281, 1217; **HRMS** (ES^-) cald for $C_{16}H_{12}O_2Br$: $(M-H)^-$ 315.0015. Found: 315.0022.



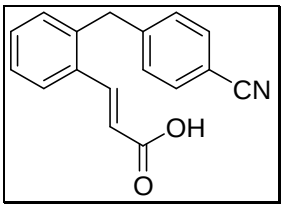
(*E*)-3-(2-(4-fluorobenzyl)phenyl)acrylic acid 135

Isolated as a colourless solid in a 69% yield. **m.p.** (hexanes) 147 ºC; **^{1}H NMR** (DMSO, 360 MHz) δ 7.86 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.76 (d, 1H, Ar*H*, J = 7.9 Hz), 7.41 (m, 1H, Ar*H*), 7.33 (t, 2H, Ar*H*, J = 7.3 Hz), 7.18 - 7.09 (m, 4H, Ar*H*), 6.41 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.16 (s, 2H, ArCH_2); **^{13}C NMR** (DMSO, 91 MHz) δ 167.3 (quat), 161.9, 159.3 (CF), 141.0 (CH), 139.8 (quat), 136.6 (quat), 132.9 (quat), 130.8 (CH), 130.2 (CH), 130.1 (CH), 130.0 (CH), 127.1 (CH), 126.9 (CH), 120.5 (CH), 115.3 (CH), 115.1 (CH), 37.2 (CH_2); **IR** (film/cm^{-1}) 1680, 1621, 1509, 1224; **HRMS** (ES^-) cald for $C_{16}H_{12}O_2F$: $(M-H)^-$ 255.0816. Found: 255.0809.



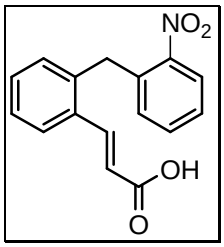
(*E*)-3-(2-(3-chlorobenzyl)phenyl)acrylic acid 136

Isolated as a white powdery solid in a yield of 91%. **m.p.** (hexanes) 142 ºC; **^{1}H NMR** (DMSO, 360 MHz) δ 7.86 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.77 (dd, 1H, Ar*H*, J = 8.7, 1.7), 7.43 (m, 1H, Ar*H*), 7.36 - 7.30 (m, 3H, Ar*H*), 7.26 (m, 1H, Ar*H*), 7.18 (t, 1H, Ar*H*, J = 1.7 Hz), 7.09 (bd, 1H, Ar*H*, J = 7.6 Hz), 6.41 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.18 (s, 2H, ArCH_2); **^{13}C NMR** (DMSO, 91 MHz) δ 167.2 (quat), 143.0 (quat), 140.9 (CH), 139.1 (quat), 133.0 (quat), 132.9 (quat), 130.8 (CH), 130.2 (CH), 128.1 (CH), 127.2 (CH), 127.0 (CH), 126.9 (CH), 126.0 (CH), 120.6 (CH), 37.5 (CH_2); **IR** (film/cm^{-1}) 1681, 1621, 1416, 1279, 1223; **HRMS** (ES^-) cald for $C_{16}H_{12}O_2Cl$: $(M-H)^-$ 271.0520. Found: 271.0512.



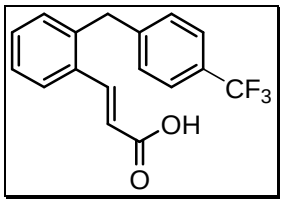
(*E*)-3-(2-(4-cyanobenzyl)phenyl)acrylic acid 137

Isolated as a colourless powdery solid in a yield of 89%. **m.p.** (hexanes) 175 ºC; **^{1}H NMR** (DMSO, 360 MHz) δ 7.95 - 7.76 (m, 4H, Ar*H*), 7.44 - 7.30 (m, 5H, Ar*H*), 6.41 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.27 (s, 2H, ArCH_2); **^{13}C NMR** (DMSO, 91 MHz) δ 168.7 (quat), 148.0 (quat), 142.3 (CH), 140.2 (quat), 134.5 (quat), 133.9 (CH), 132.5 (CH), 131.8 (CH), 128.9 (CH), 128.5 (CH), 122.2 (CH), 120.3 (quat), 110.4 (quat), 39.5 (CH_2); **IR** (film/cm^{-1}) 2360, 2341, 1677, 1623; **HRMS** (ES^-) cald for $C_{17}H_{12}NO_2$: $(M-H)^-$ 262.0862. Found: 262.0867.



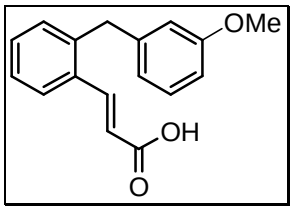
(*E*)-3-(2-(2-nitrobenzyl)phenyl)acrylic acid 138

Isolated as a powdery yellow solid in a yield of 58%. **m.p.** (hexanes) 157 ºC; **^{1}H NMR** (DMSO, 360 MHz) δ 8.05 (d, 1H, Ar*H*, J = 7.5 Hz), 7.82 - 7.78 (m, 2H, Ar*H*), 7.67 (t, 1H, Ar*H*, J = 6.9 Hz), 7.55 (t, 1H, Ar*H*, J = 7.5 Hz), 7.36 - 7.31 (m, 2H, Ar*H*), 7.21 (d, 1H, Ar*H*, J= 7.6 Hz), 7.00 (d, 1H, Ar*H*, J = 8.6 Hz), 6.43 (d, 1H, CH=C*H*, J = 15.7 Hz), 4.46 (s, 2H, ArCH_2); **^{13}C NMR** (DMSO, 91 MHz) δ 167.2 (quat), 148.8 (quat), 140.6 (CH), 137.8 (quat), 134.3 (quat), 133.6 (CH), 133.2 (quat), 132.0 (CH), 130.2 (CH), 129.8 (CH), 128.0 (CH), 127.3 (CH), 127.0(CH), 124.8 (CH), 121.0 (CH), 34.6 (CH_2); **IR** (film/cm^{-1}) 1699, 1634, 1523, 1348; **HRMS** (ES^-) cald for $C_{16}H_{12}NO_4$: $(M-H)^-$ 282.0761. Found: 282.0763.



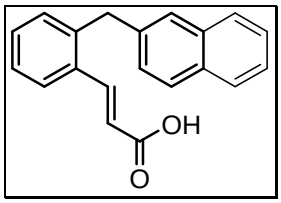
(***E*)-3-(2-(4-(trifluoromethyl)benzyl)phenyl)acrylic acid 139**

Isolated as a colourless crystalline solid in a yield of 67%. **m.p.** (water) 122 – 123 ºC; **^{1}H NMR** (DMSO, 360 MHz) δ 7.85 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.79 (d, 1H, Ar*H*, J = 7.3 Hz), 7.67 (d, 2H, Ar*H*, J = 8.1 Hz), 7.42 (q, 1H, Ar*H*, J = 7.2 Hz), 7.36 - 7.33 (m, 4H, Ar*H*), 6.42 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.27 (s, 2H, ArCH_2); **^{13}C NMR** (DMSO, 91 MHz) δ 167.2 (quat), 145.4 (quat), 140.9 (CH), 139.0 (quat), 133.0 (quat), 131.0 (CH), 130.3 (CH), 129.1 (CH), 127.3 (CH), 127.0 (CH), 127.6 (CF_3) 125.3 (CH), 120.6 (CH), 37.8 (CH_2); **^{19}F NMR** (DMSO, 235 MHz) δ -62.0; **IR** (film/cm^{-1}) 1699, 1633, 1325, 1164, 1122, 1066; **HRMS** (ES^-) cald for $C_{17}H_{12}O_2F_3$: $(M-H)^-$ 305.0784. Found: 305.0798.



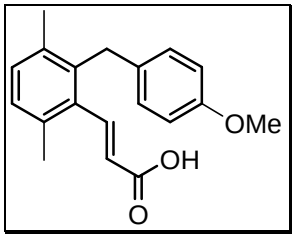
(*E*)-3-(2-(3-methoxybenzyl)phenyl)acrylic acid 140

Isolated as a colourless crystalline solid in a yield of 62%. **m.p** (water) 134 – 135 ºC; **^{1}H NMR** (DMSO, 360 MHz) δ 7.91 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.76 (d, 1H, Ar*H*, J = 7.7 Hz), 7.40 (q, 1H, Ar*H*, J = 8.3 Hz), 7.33 - 7.30 (m, 2H, Ar*H*), 7.20 (t, 1H, Ar*H*, J = 7.7 Hz), 7.78-6.67 (m, 3H, Ar*H*), 6.41 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.11 (s, 2H, ArCH_2), 3.71 (s, 3H, OCH_3); **^{13}C NMR** (DMSO, 91 MHz) δ 167.4 (quat), 159.3 (quat), 142.0 (quat), 141.2 (CH), 139.9 (quat), 132.9 (quat), 130.9 (CH), 130.2 (CH), 129.5 (CH), 127.1 (CH), 126.8 (CH), 120.6 (CH) 120.3 (CH), 114.2 (CH), 111.3 (CH), 54.8 (CH_3), 38.1 (CH_2); **IR** (film/cm^{-1}) 1681, 1620, 1279, 1222;. **HRMS** (ES$^-$) cald for $C_{17}H_{15}O_3$: (M-H)$^-$ 267.1016. Found: 267.1016.



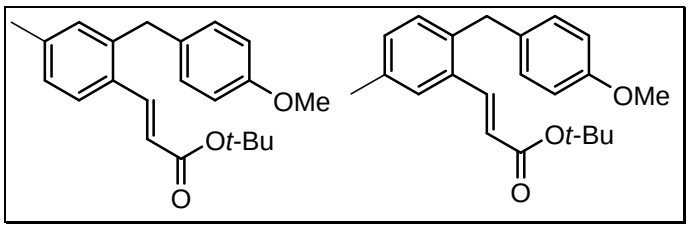
(*E*)-3-(2-((naphthalen-3-yl)methyl)phenyl)acrylic acid 141

Isolated as a colourless powdery solid in a yield of 92%. **m.p.** (hexane) 160-161 ºC; **^{1}H NMR** (DMSO, 360 MHz) δ 7.96 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.88 - 7.78 (m, 4H, Ar*H*), 7.50 (s, 1H, Ar*H*), 7.48 - 7.32 (m, 6H, Ar*H*), 6.41 (d, 1H, CH=C*H*, J = 15.8 Hz), 4.32 (s, 2H, ArCH_2); **^{13}C NMR** (DMSO, 91 MHz) δ 167.4 (quat), 141.3 (CH), 139.8 (quat), 138.2 (quat), 133.1 (quat), 133.0 (quat), 131.6 (quat), 131.0 (CH), 130.3 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 126.4 (CH), 126.2 (CH), 125.6 (CH), 120.4 (CH), 38.3 (CH_2); **IR** (film/cm^{-1}) 2977, 1740, 1707, 1321, 1150; **HRMS** (ES$^-$) cald for $C_{20}H_{15}O_2$: (M-H)$^-$ 287.1077. Found: 287.1070.



(E)-3-(2-(4-methoxybenzyl)-3,6-dimethylphenyl)acrylic acid 142

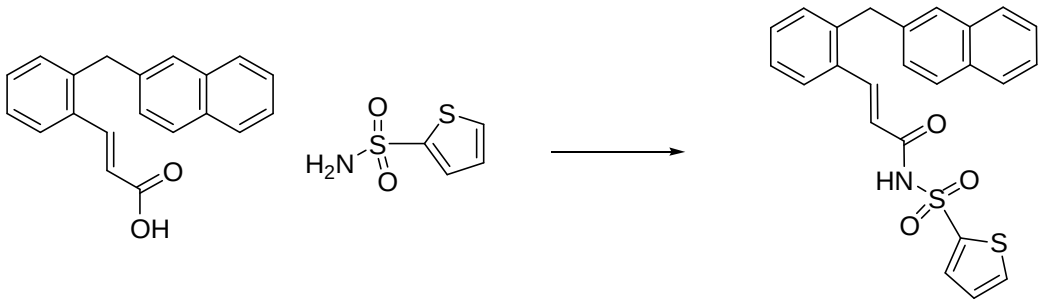
Isolated as a colourless oily solid in a yield of 76%. **^{1}H NMR** (DMSO, 400 MHz) δ 7.08 (d, 1H, CH=C*H*, J = 16.2 Hz), 7.01 – 6.94 (dd, 2H, Ar*H*, J = 7.7, 20.3 Hz), 6.87 – 6.79 (dd, 4H, Ar*H*, J = 8.7, 25.5 Hz), 5.72 (d, 1H, CH=C*H*, J = 16.2 Hz), 3.94 (s, 2H, ArCH_2), 3.69 (s, 3H, OCH_3), 2.23 (s, 3H, ArCH_3), 2.04 (s, 3H, ArCH_3); **^{13}C NMR** (DMSO, 91 MHz) δ 169.0 (quat), 157.1 (quat), 137.7 (quat), 136.6 (CH), 136.0 (quat), 133.8 (quat), 132.8 (quat), 132.5 (CH), 132.0 (quat), 128.5 (2C, CH), 128.3 (CH), 127.9 (CH), 113.6 (2C, CH), 54.3 (CH_3), 34.3 (CH_2), 20.8 (CH_3), 19.3 (CH_3); **IR** (film/cm^{-1}) 2977, 1740, 1708, 1642, 1319, 1212.



(*E*)-tert-butyl 3-(2-(4-methoxybenzyl)-4-methylphenyl)acrylate 143 and (*E*)-tert-butyl 3-(2-(4-methoxybenzyl)-5-methylphenyl)acrylate 144

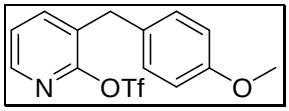
Isolated as a colourless oil in a yield of 70%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.92 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.50 (d, 0.5 H, Ar*H*, J = 7.9 Hz), 7.41 (bs, 0.5 H, Ar*H*), 7.19 - 7.12 (m, 3.5H, Ar*H*), 7.02 (bs, 0.5H, Ar*H*), 6.85 - 6.80 (m, 2H, Ar*H*), 6.26 (d, 0.5H, CH=C*H*, J = 15.8 Hz), 6.24 (d, 0.5H, CH=C*H*, J = 15.8 Hz), 4.05 (s, 2H, ArCH_2), 3.77 (s, 3H, OCH_3), 1.53 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 166.3 (quat), 166.2 (quat), 157.8 (quat), 157.8 (quat), 141.2 (quat), 141.0 (quat), 140.3 (CH), 140.0 (CH), 137.5 (quat), 136.1 (quat), 133.3 (quat), 132.5 (quat), 132.4 (quat), 131.3 (CH), 130.7 (CH), 130.6 (CH), 130.5 (CH), 129.5 (CH), 127.6 (CH), 127.1 (CH), 126.5 (CH), 121.2 (CH), 120.4 (CH), 113.8 (CH), 80.2 (quat), 80.2 (quat), 55.1 (CH_3), 38.0 (CH_2), 37.7 (CH_2), 28.1 (CH_3), 21.3 (CH_3), 20.9 (CH_3); **IR**

(film/cm^{-1}) 2977, 1707, 1511, 1248, 1150; **HRMS** (ES^+) cald for $C_{18}H_{17}O_2$: $(M\text{-}O^tBu)^+$ 265.1223. Found: 265.1213.



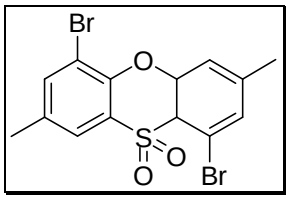
Thiophene-2-sulfonic acid [3-(2-naphthalen-2-ylmethylphenyl)-acryloyl]-amide 158

Thiophene-2-sulfonamide (30 mg, 1.1 equiv.), (E)-3-(2-((naphthalen-3-yl)methyl)phenyl)acrylic acid (48 mg, 1 equiv.) and DMAP (43 mg, 2 equiv.) were taken up in DCM (1.5 mL) in a carousel tube. EDCI (69 mg, 2 equiv.) was added and the reaction stirred overnight at room temperature. DCM and HCl (1M) were added and the organic then washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification on silica, eluting with DCM, yielded the title compound as a white crystalline solid, 48 mg, 67%. **^{1}H NMR** (DMSO, 360 MHz) δ 8.06 (dd, 1H, Ar*H*, J = 1.4, 5.0 Hz), 7.99 (d, 1H, CH=C*H*, J = 15.7 Hz), 7.85 – 7.79 (m, 3H, Ar*H*), 7.71 (m, 1H, Ar*H*), 7.60 – 7.55 (m, 2H, Ar*H*), 7.47 – 7.27 (m, 6H, Ar*H*), 7.22 (dd, 1H, Ar*H*, J = 3.8, 5.0 Hz), 6.48 (d, 1H, CH=C*H*, J = 15.6 Hz), 4.28 (s, 2H, CH_2); **^{13}C NMR** (DMSO, 91 MHz) δ 163.2 (quat), 141.4 (CH), 140.5 (quat), 139.5 (quat), 138.0 (quat), 134.8 (CH), 134.3 (CH), 133.0 (quat), 132.7 (quat), 131.5 (quat), 131.0 (CH), 130.7 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 127.2 (CH), 126.6 (CH), 126.4 (CH), 126.2 (CH), 125.5 (CH), 120.1 (CH), 38.2 (CH_2).



3-(4-methoxybenzyl)pyridin-2-yl trifluoromethanesulfonate 171

Isolated as a slightly yellow oil in a yield of 45% from attempted three component coupling of 3-(trimethylsilyl)pyridin-2-yl trifluoromethanesulfonate **166** with 4-methoxybenzyl bromide and *tert*-butyl actylate. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 8.28 (dd, 1H, Ar*H*, J = 2.2, 7.4 Hz), 7.72 (dd, 1H, Ar*H*, J = 2.2, 6.7 Hz), 7.30 (d, 2H, Ar*H*, J = 8.8 Hz), 6.92 (d, 2H, Ar*H*, J = 8.8 Hz), 6.37 (dd, 1H, Ar*H*, J = 6.7, 7.4 Hz), 5.13 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 160.1 (quat), 157.0 (quat), 148.6 (CH), 146.3 (CH), 130.6 (2C, CH), 126.0 (quat), 114.7 (2C, CH), 113.9 (quat) 104.8 (CH), 55.3 (CH_3), 52.4 (CH_2); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -76.9 (s); **IR** (film/cm^{-1}) 3400, 1664, 1530, 1513, 1360, 1209; **HRMS** (EI^+) cald for $C_{14}H_{12}F_3NO_4S$: $(M+H)^+$ 347.0433. Found: 347.0432.

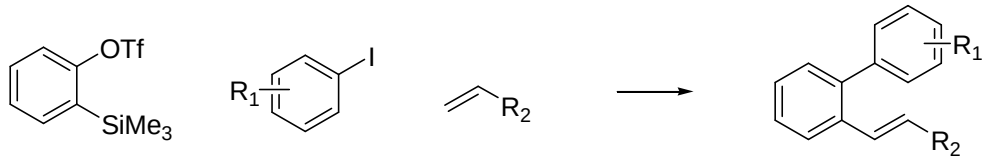


1,6-Dibromo-3,8-dimethyl-phenoxathiin 10,10-dioxide 173

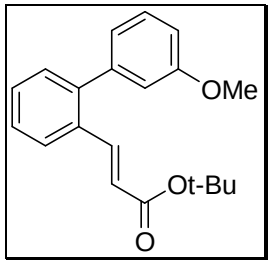
Isolated as colourless needle-like crystals in a yield of 58% from attempted three component coupling of 2-bromo-4-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **168** with methyl bromoacetate and *tert*-butyl actylate, in a yield of 55% upon reaction of **168** with $Pd(OAc)_2$ (5 mol%), P(*o*-tol)$_3$ (10 mol%) and CsF (3 equiv.) in MeCN at 45 ºC for 4 hours or in a yield of 52% using CsF (3 equiv.) in MeCN at 45 ºC for 4 hours. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.79 (s, 1H, Ar*H*), 7.69 (s, 1 H, Ar*H*), 7.43 (s, 1H, Ar*H*), 7.26 (s, 1H, Ar*H*), 2.44 (s, 6H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 151.7 (quat), 145.6 (quat), 144.3 (quat), 138.4 (CH), 136.1 (quat), 132.1 (CH), 125.9 (quat), 122.6 (CH), 121.2 (quat), 118.9 (CH), 117.2 (quat), 111.3 (quat), 21.6 (CH_3), 20.6 (CH_3); **IR** (film/cm^{-1}) 3433, 2925, 1598, 1467, 1302, 1148; **HRMS** (ES^+) cald for $C_{14}H_{11}{}^{79}Br_2O_3$: $(M+H)^+$ 416.87956. Found: 416.87968.

6.4 Aryl Heck Reactions

6.4.1 General method for 3-component coupling involving aryl iodides

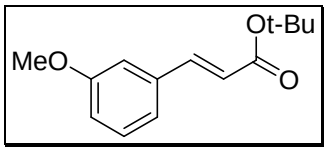


The aryl iodide (0.31 mmol, 1.5 equiv.) was added to a stirred suspension of $Pd(OAc)_2$ (2 mg, 5 mol %), P(*o*-tol)$_3$ (6.1 mg, 10 mol %) and CsF (6 equiv.) in dry MeCN (1 mL) under N_2 in a carousel tube and heated to 45 ºC. This was followed by the addition of *tert*-butyl acrylate (0.21 mmol, 1 equiv.) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1** (0.21 mmol, 1 equiv.). The reaction was stirred at 45 ºC for 1 hour after which a second portion of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1** (0.21 mmol, 1 equiv.) was added. The reaction was stirred for a further 3 hours. The reaction was diluted with DCM and filtered through a short plug of silica then concentrated. Purification on silica, eluting with 30% - 50% DCM/hexanes yielded the title compounds.



(E)-3-(3'-Methoxy-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 185

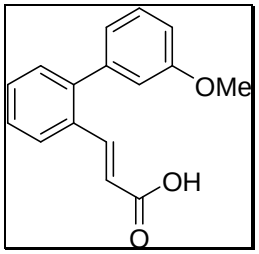
Isolated as a colourless oil by SFC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69 – 7.64 (m, 2H, CH=C*H*, Ar*H*), 7.41 – 7.31 (m, 4H, Ar*H*), 6.93 – 6.85 (dt, 2H, Ar*H*, J = 2.4, 8.8 Hz), 6.32 (d, 1H, Ar*H*, J = 2.0 Hz), 6.32 (d, 1H, CH=C*H*, J = 16.0 Hz), 3.83 (s, 3H, OCH_3), 1.47 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.2 (quat), 159.7 (quat), 142.9 (quat), 142.6 (CH), 141.6 (quat), 133.1 (quat), 130.4 (CH), 129.5 (CH), 129.3 (CH), 127.7 (CH), 126.7 (CH), 122.5 (CH), 121.3 (CH), 115.6 (CH), 113.6 (CH), 80.3 (quat), 55.4 (CH_3), 28.3 (3C, CH_3); **IR** (film/cm^{-1}) 2976, 1707, 1632, 1473, 1321, 1222.



(E)-tert-butyl 3-(3-methoxyphenyl)acrylate 186

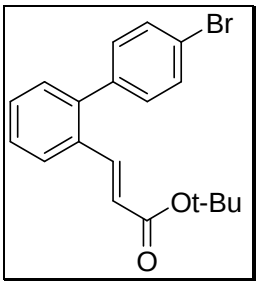
Isolated as a colourless oil by SFC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.55 (d, 1H, CH=C*H*, J = 15.9 Hz), 7.28 (t, 1H, Ar*H*, J = 7.6 Hz), 7.09 (d, 1H, Ar*H*, J = 7.6 Hz), 7.02 (t, 1H, Ar*H*, J = 2.0 Hz), 6.91 (dd, 1H, Ar*H*, J = 7.6, 2.0 Hz), 6.35 (d, 1H, CH=C*H*, J = 15.9 Hz), 3.82 (s, 3H, OCH_3), 1.53 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.1 (quat), 159.7 (quat), 143.3 (CH), 135.9 (quat), 129.6 (CH), 120.5 (CH), 120.3 (CH), 115.7 (CH), 112.7 (CH), 80.3 (quat), 55.1 (CH_3), 28.0 (3C, CH_3).

The spectroscopic data was in agreement with that previously published.[201]



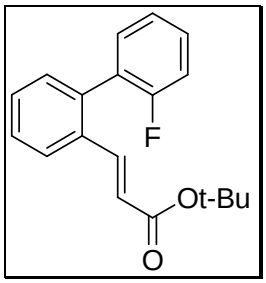
(E)-3-(3'-Methoxy-biphenyl-2-yl)-acrylic acid 187 (acid of 185)

Isolated in a yield of 53%, following treatment of the esters **185** and **186** with TFA/DCM 1:1 overnight at room temperature. Concentration *in vacuo* and recrystallization from EtOAc afforded the acid as a colourless solid. **m.p.** (DCM) 131 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.68 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.63 (d, 2H, Ar*H*, J = 7.6 Hz), 7.39 – 7.27 (m, 4H, Ar*H*), 6.89 – 6.80 (m, 3H, Ar*H*), 6.33 (d, 1H, CH=C*H*, J = 15.9 Hz), 3.76 (s, 3H, OCH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.0 (quat), 159.5 (quat), 146.1 (CH), 143.1 (quat), 141.1 (quat), 132.2 (quat), 130.4 (CH), 130.2 (CH), 129.3 (CH), 127.8 (CH), 127.0 (CH), 122.4 (CH), 118.1 (CH), 115.4 (CH), 113.5 (CH), 55.3 (CH_3); **IR** (film/cm^{-1}) 2300, 1707, 1626, 1472, 1421, 1320, 1214; **HRMS** (ES^+) cald for $C_{16}H_{14}O_3$: $(M+H)^+$ 254.09375. Found: 254.09491.



(E)-3-(4'-Bromo-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 188

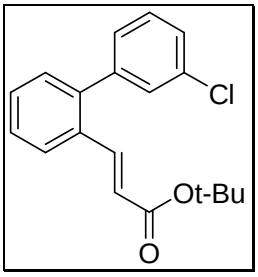
Isolated in a yield of 63% as a colourless solid. **m.p.** (DCM) 52 - 54 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.70 (d, 1H, Ar*H*, J = 7.6 Hz), 7.61 – 7.55 (m, 3H, CH=C*H*, Ar*H*), 7.44 – 7.36 (m, 2H, Ar*H*), 7.32 (m, 1H, Ar*H*), 7.19 (d, 2H, Ar*H*, J = 8.4 Hz), 6.34 (d, 1H, CH=C*H*, J = 16.0 Hz), 1.49 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.1 (quat), 142.0 (CH), 141.6 (quat), 138.9 (quat), 132.7 (quat), 131.4 (2C, CH), 131.4 (2C, CH), 130.3 (CH), 129.7 (CH), 127.9 (CH), 126.7 (CH), 121.9 (quat), 121.3 (CH), 80.5 (quat), 28.2 (3C, CH_3); **IR** (film/cm^{-1}) 1707, 1632, 1474, 1321, 1150; **HRMS** (ES^+) cald for $C_{19}H_{19}$ $^{81}BrO_2$: $(M+H)^+$ 360.05425. Found: 360.05424.



(E)-3-(2'-Fluoro-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 189

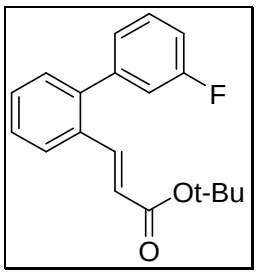
Isolated in a yield of 51% as a colourless solid. **m.p.** (DCM) 70 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.74 (m, 1H, Ar*H*), 7.49 (dd, 1H, Ar*H*, J = 1.6, 16.0 Hz), 7.44 – 7.32 (m, 4H, Ar*H*), 7.24 – 7.21 (m, 2H, Ar*H*), 7.16 (m, 1H, Ar*H*) 6.33 (d, 1H, CH=C*H*, J = 16.0 Hz), 1.46 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.1 (quat), 159.6 (d, CF, J = 246.9 Hz), 141.6 (CH), 136.6 (quat), 133.5 (quat), 132.1 (d, CH, J = 4.0 Hz), 131.0 (CH), 129.8 (d, CH, J = 8.1 Hz), 129.5 (CH), 128.3 (CH), 127.4 (d, quat, J = 16.0 Hz), 126.2 (CH), 124.1 (d, CH, J = 3.7 Hz), 121.2 (CH), 115.8 (d, CH, J = 22.3 Hz), 80.3 (quat), 28.2 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 376

MHz) δ -115.1; **IR** (film/cm^{-1}) 2978, 1708, 1634, 1322, 1207, 1150; **HRMS** (ES^+) cald for $C_{19}H_{19}FO_2$: $(M+H)^+$ 298.13636. Found: 298.13563.



(E)-3-(3'-Chloro-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 190

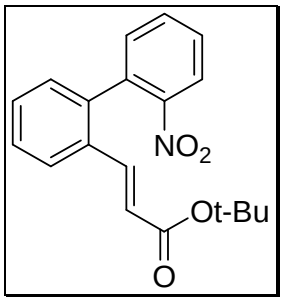
Isolated in a yield of 73% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.70 (m, 1H, Ar*H*), 7.59 (d, 1H, CH=C*H*, J = 15.9 Hz), 7.42 – 7.31 (m, 6H, Ar*H*), 7.19 (m, 1H, Ar*H*), 6.33 (d, 1H, CH=C*H*, J = 15.9 Hz), 1.49 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.0 (quat), 141.8 (CH), 141.3 (quat), 134.2 (quat), 132.7 (quat), 130.3 (CH), 129.7 (CH), 129.6 (CH), 129.4 (CH), 128.1 (CH), 127.6 (CH), 126.7 (CH), 121.5 (CH), 80.4 (quat), 28.1 (3C, CH_3); **IR** (film/cm^{-1}) 2977, 1709, 1633, 1466, 1367, 1321, 1151; **HRMS** (ES^+) cald for $C_{15}H_{10}{}^{35}ClO_2$: $(M-{}^tBu)^+$ 257.03638. Found: 257.03584.



(E)-3-(3'-Fluoro-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 191

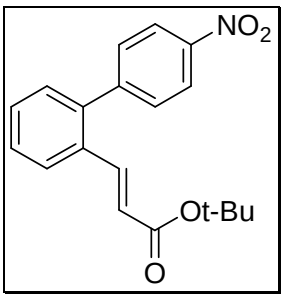
Isolated in a yield of 74% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.70 (dd, 1H, Ar*H*, J = 1.6, 7.2 Hz), 7.60 (d, 1H, CH=C*H*, J = 15.6 Hz), 7.44 – 7.32 (m, 4H, Ar*H*), 7.09 (dd, 2H, Ar*H*, J = 2.4, 8.0 Hz), 7.04 (m, 1H, Ar*H*), 6.33 (d, 1H, CH=C*H*, J = 16.0 Hz) 1.48 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (**$CDCl_3$, 101 MHz) δ 166.0 (quat), 162.6 (CF, d, J = 246.5 Hz), 142.2 (quat, d, J = 7.7 Hz), 141.9 (CH), 141.5 (quat), 132.7 (quat), 130.3 (CH), 129.7 (CH, d, J = 8.5 Hz), 129.6 (CH) 128.0 (CH), 126.7 (CH), 125.6 (CH, d, J = 2.9 Hz), 121.4 (CH), 116.7 (CH, d, J = 21.7 Hz), 114.4 (CH, d, J = 21.0 Hz), 80.4 (quat), 28.1 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -

113.2; **IR** (film/cm^{-1}) 2978, 1708, 1633, 1473, 1367, 1322, 1151; **HRMS** (ES$^+$) cald for $C_{19}H_{19}FO_2$: $(M+H)^+$ 298.13636. Found: 298.13562.



(E)-3-(2'-Nitro-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 192

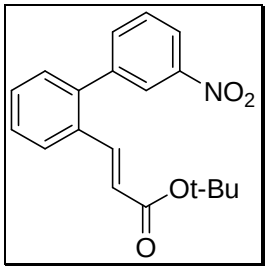
Isolated in a yield of 56% as a slightly yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.04 (dd, 1H, Ar*H*, J = 0.8, 8.0 Hz), 7.72 (m, 1H, Ar*H*), 7.65 (dt, 1H, Ar*H*, J = 1.0, 7.2 Hz), 7.55 (dt, 1H, Ar*H*, J = 1.2, 7.8 Hz), 7.43 – 7.37 (m, 2H, CH=C*H*, Ar*H*), 7.34 – 7.30 (m, 2H, Ar*H*), 7.19 – 7.17 (m, 1H, Ar*H*), 6.30 (d, 1H, CH=C*H*, J = 15.6 Hz), 1.45 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 165.8 (quat), 149.2 (quat), 140.5 (CH), 138.4 (quat), 134.9 (quat), 132.9 (quat), 132.7 (CH), 132.6 (CH), 129.6 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 126.3 (CH), 124.5 (CH), 121.9 (CH), 80.5 (quat) 28.1 (3C, CH_3); **IR** (film/cm^{-1}) 2978, 1706, 1634, 1574, 1351, 1323, 1150; **HRMS** (ES$^+$) cald for $C_{19}H_{19}NO_4$: $(M+H)^+$ 325.13086. Found: 325.12939.



(E)-3-(4'-Nitro-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 193

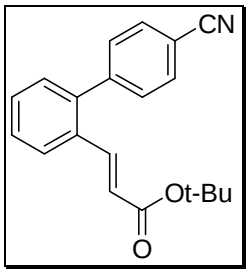
Isolated in a yield of 60% as a colourless solid. **m.p.** (DCM) 154 – 156 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.30 (d, 2H, Ar*H*, J = 8.8 Hz), 7.73 (m, 1H, Ar*H*), 7.53 – 7.44 (m, 5H, CH=C*H*, Ar*H*), 7.34 (m, 1H, Ar*H*), 6.36 (d, 1H, CH=C*H*, J = 15.8 Hz), 1.48 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 165.8 (quat), 147.3 (quat), 146.8 (quat), 141.2 (CH), 140.3 (quat), 132.8 (quat), 130.7 (2C, CH), 130.1 (CH), 129.8 (CH), 128.9 (CH), 127.0 (CH), 123.5 (2C, CH), 122.2 (CH), 80.7 (quat), 28.2 (3C, CH_3); **IR** (film/cm^{-1}) 1703, 1631, 1593, 1514, 1366, 1151; **HRMS** (ES$^+$) cald for

$C_{19}H_{19}NO_4$: $(M+H)^+$ 325.13086. Found: 325.13030; **Anal.** cald for $C_{19}H_{19}NO_4$: %C 70.14, %H 5.89, %N 4.31. Found %C 70.05, %H 5.79, %N 4.28.



(E)-3-(3'-Nitro-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 194

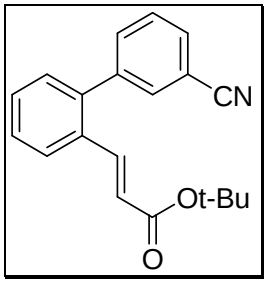
Isolated in a yield of 85% as a colourless solid. **m.p.** (DCM) 143 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.27 – 8.21 (m, 2H, Ar*H*), 7.72 (m, 1H, Ar*H*), 7.66 – 7.60 (m, 2H, Ar*H*), 7.50 (d, 1H, CH=C*H*, J = 16.0 Hz), 7.47 – 7.44 (m, 2H, Ar*H*), 7.36 (m, 1H, Ar*H*), 6.36 (d, 1H, CH=C*H*, J = 16.0 Hz), 1.47 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 165.8 (quat), 148.3 (quat), 141.7 (quat), 141.1 (CH), 140.0 (quat), 135.8 (CH), 132.9 (quat), 130.3 (CH), 129.9 (CH), 129.2 (CH), 128.7 (CH), 127.0 (CH), 124.5 (CH), 122.4 (CH), 122.3 (CH), 80.6 (quat), 28.1 (3C, CH_3); **IR** (film/cm^{-1}) 1707, 1633, 1530, 1351, 1322; **HRMS** (ES^+) cald for $C_{19}H_{19}NO_4$: $(M+H)^+$ 325.13086. Found: 325.13082.



(E)-3-(4'-Cyano-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 195

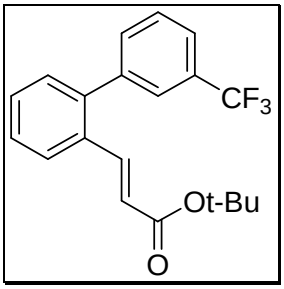
Isolated in a yield of 64% as a colourless solid. **m.p.** (DCM) 127 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.74 – 7.71 (m, 3H, Ar*H*), 7.51 (d, 1H, CH=C*H*, J = 15.9 Hz), 7.46 – 7.43 (m, 4H, Ar*H*), 7.32 (m, 1H, Ar*H*), 6.35 (d, 1H, CH=C*H*, J = 15.9 Hz), 1.48 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 165.9 (quat), 144.8 (quat), 141.3 (CH), 140.7 (quat), 132.7 (quat), 132.1 (2C, CH), 130.5 (2C, CH), 130.1 (CH), 129.8 (CH), 128.7 (CH), 127.0 (CH), 122.0 (CH), 118.7 (quat), 111.5 (quat), 80.7 (quat), 28.1 (3C, CH_3); **IR** (film/cm^{-1}) 1706, 1634, 1475, 1367, 1323, 1150; **HRMS**

(ES^+) cald for $C_{20}H_{19}NO_2$: $(M+H)^+$ 305.14103. Found: 305.14120; **Anal.** cald for $C_{20}H_{19}NO_2$: %C 78.66, %H 6.27, %N 4.59. Found %C 78.67, %H 6.56, %N 4.74.



(E)-3-(3'-Cyano-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 196

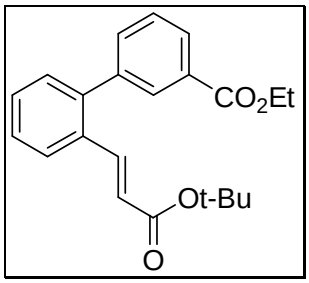
Isolated in a yield of 90% as a colourless solid. **m.p.** (DCM) 93 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.73 – 7.70 (m, 2H, Ar*H*), 7.62 (bs, 1H, Ar*H*), 7.56 – 7.55 (m, 2H, Ar*H*), 7.48 (d, 1H, CH=C*H*, J = 16.0 Hz), 7.44 – 7.41 (m, 2H, Ar*H*), 7.31 (m, 1H, Ar*H*) 6.35 (d, 1H, CH=C*H*, J = 15.6 Hz), 1.48 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 165.8 (quat), 141.3 (quat), 141.2 (CH), 140.2 (quat), 134.2 (CH), 133.1 (CH), 132.7 (quat), 131.1 (CH), 130.2 (2C, CH), 129.9 (CH), 128.6 (CH), 126.9 (CH), 122.1 (CH), 118.6 (quat), 112.6 (quat), 80.7 (quat), 28.1 (3C, CH_3); **IR** (film/cm^{-1}) 2978, 1706, 1633, 1472, 1367, 1322, 1150; **HRMS** (ES^+) cald for $C_{20}H_{19}NO_2$: $(M+H)^+$ 305.14103. Found: 305.14073.



(E)-3-(3'-Trifluoromethyl-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 197

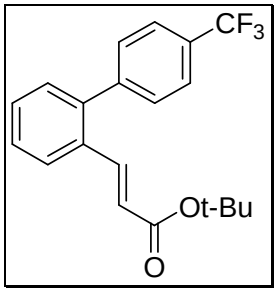
Isolated in a yield of 63% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.71 (m, 1H, Ar*H*), 7.65 (d, 1H, Ar*H*, J = 7.6 Hz), 7.59 – 7.54 (m, 4H, Ar*H*), 7.43 (dquint, 2H, Ar*H*, J = 2.1, 6.7 Hz), 7.35 (m, 1H, Ar*H*), 6.34 (d, 1H, CH=C*H*, J = 16.0 Hz), 1.47 (s, 9H, CCH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 165.9 (quat), 141.6 (CH), 141.1 (quat), 140.8 (quat), 133.1 (CH), 132.9 (quat), 130.8 (d, quat, J = 32.3 Hz), 130.3 (CH), 129.7 (CH), 128.7 (CH), 128.3 (CH), 126.8 (CH), 126.5 (q, CH, J = 3.7 Hz), 124.3

(q, CH, J = 3.7 Hz), 124.1 (q, CF_3, J = 272.4 Hz), 121.9 (CH), 80.5 (quat), 28.1 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -62.8; **IR** (film/cm^{-1}) 2979, 1709, 1633, 1335, 1151, 1129; **HRMS** (ES^+) cald for $C_{20}H_{19}F_3O_2$: $(M+H)^+$ 348.13317. Found: 348.13270.



2'-((E)-2-*tert*-Butoxycarbonyl-vinyl)-biphenyl-3-carboxylic acid ethyl ester 198

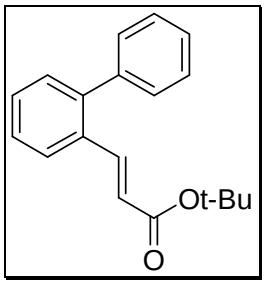
Isolated in a yield of 70% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.07 (m, 1H, Ar*H*), 8.02 (s, 1H, Ar*H*), 7.71 (d, 1H, Ar*H*, J = 7.2 Hz), 7.56 (d, 1H, CH=C*H*, J = 16.0 Hz), 7.51 – 7.50 (m, 2H, Ar*H*), 7.44 – 7.36 (m, 3H, Ar*H*) 6.33 (d, 1H, CH=C*H*, J = 16.0 Hz), 4.39 (q, 2H, C*H*$_2$CH$_3$, J = 7.1 Hz), 1.46 (s, 9H, C(C*H*$_3$)$_3$), 1.39 (t, 3H, CH$_2$C*H*$_3$, J = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.4 (quat), 166.0 (quat), 141.9 (CH), 141.8 (quat), 140.3 (quat), 134.2 (CH), 132.8 (quat), 130.7 (CH), 130.6 (CH), 130.4 (CH), 129.7 (CH), 128.7 (CH), 128.2 (CH), 128.0 (CH), 126.7 (CH), 121.5 (CH), 80.4 (quat), 61.0 (CH_2), 28.1 (3C, CH_3), 14.3 (CH_3); **IR** (film/cm^{-1}) 2979, 1706, 1633, 1472, 1367, 1239, 1150; **HRMS** (ES^+) cald for $C_{18}H_{16}O_4$: $(M-{}^tBu)^+$ 296.10431. Found: 296.10316.



(E)-3-(4'-Trifluoromethyl-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 199

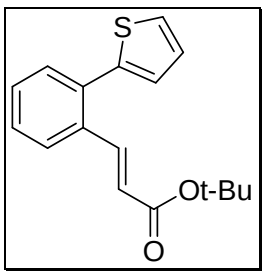
Isolated in a yield of 86% as a colourless oily solid. **m.p.** (DCM) 59 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.74 – 7.69 (m, 3H, Ar*H*), 7.56 (d, 1H, CH=C*H*, J = 16.0 Hz), 7.45 – 7.41 (m, 4H, Ar*H*), 7.34 (dd, 1H, Ar*H*, J = 1.8, 7.0 Hz), 6.36 (d, 1H, CH=C*H*,

J = 16.0 Hz) 1.48 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.0 (quat), 143.7 (quat), 141.6 (CH), 141.3 (quat), 132.7 (quat), 130.3 (CH), 130.1 (2C, CH), 129.7 (CH), 129.7 (quat, d, J = 32.5 Hz) 128.3 (CH), 126.8 (CH), 125.2 (CH), 125.2 (CH), 124.2 (CF_3, q, J = 271.9 Hz), 121.7 (CH), 80.6 (quat) 28.1 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -62.5; **IR** (film/cm^{-1}) 2979, 1708, 1634, 1321, 1152, 1127; **HRMS** (ES^+) cald for $C_{20}H_{19}F_3O_2$: $(M+H)^+$ 348.13317. Found: 348.13285.



(E)-3-Biphenyl-2-yl-acrylic acid *tert*-butyl ester 200

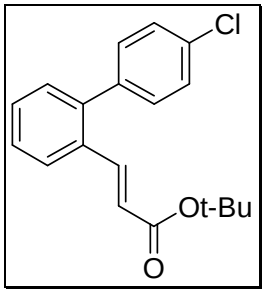
Isolated in a yield of 51% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.70 (d, 1H, Ar*H*, J = 7.2 Hz), 7.65 (d, 1H, CH=C*H*, J = 15.9 Hz), 7.45 – 7.31 (m, 8H, Ar*H*), 6.64 (d, 1H, CH=C*H*, J = 15.9 Hz), 1.48 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.3 (quat), 142.9 (quat), 142.6 (CH), 140.0 (quat), 132.7 (quat), 130.5 (CH), 129.8 (2C, CH), 129.6 (CH), 128.2 (2C, CH), 127.6 (CH), 127.5 (CH), 126.6 (CH), 120.9 (CH), 80.4 (quat), 28.2 (3C, CH_3); **IR** (film/cm^{-1}) 1708, 1632, 1367, 1321, 1151; **HRMS** (ES^+) cald for $C_{19}H_{20}O_2$: $(M+H)^+$ 280.14578. Found: 280.14702.



(E)-tert-butyl 3-(2-(thiophen-2-yl)phenyl)acrylate 201

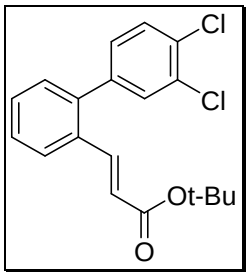
Isolated in a yield of 50% as a slightly yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.91 (d, 1H, CH=C*H*, J = 16.0 Hz), 7.66 (dd, 1H, Ar*H*, J = 1.4, 7.4 Hz), 7.49 (dd, 1H, Ar*H*, J = 1.4, 7.4 Hz), 7.41 – 7.33 (m, 3H, Ar*H*), 7.12 (dd, 1H, Ar*H*, J = 3.6, 5.2 Hz), 7.04 (dd, 1H, Ar*H*, J = 0.8, 3.6 Hz) 6.35 (d, 1H, CH=C*H*, J = 16.0 Hz), 1.52 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.2 (quat), 142.4 (CH), 141.3 (quat),

135.0 (quat), 133.4 (quat), 130.9 (CH), 129.5 (CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 127.1 (CH), 126.3 (CH), 121.7 (CH), 80.4 (quat), 28.3 (3C, CH_3); **IR** (film/cm^{-1}) 2976, 1708, 1631, 1367, 1320; **HRMS** (ES^+) cald for $C_{17}H_{18}O_2S$: $(M+H)^+$ 286.10220. Found: 286.10086.



(E)-3-(4'-Chloro-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 202

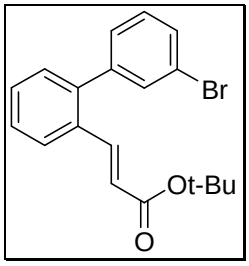
Isolated in a yield of 74% as a colourless solid. **m.p.** (DCM) 99 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.70 (d, 1H, Ar*H*, J = 7.4 Hz), 7.60 (d, 1H, CH=C*H*, J = 15.9 Hz), 7.42 – 7.38 (m, 4H, Ar*H*), 7.32 (m, 1H, Ar*H*), 7.26 – 7.24 (m, 2H, Ar*H*), 6.35 (d, 1H, CH=C*H*, J = 16.0 Hz), 1.49 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.1 (quat), 142.0 (CH), 141.5 (quat), 138.4 (quat), 133.7 (quat), 132.7 (quat), 131.0 (2C, CH), 130.3 (CH), 129.7 (CH), 128.5 (2C, CH), 127.9 (CH), 126.7 (CH), 121.3 (CH), 80.5 (quat), 28.2 (3C, CH_3); **IR** (film/cm^{-1}) 2977, 1708, 1632, 1474, 1367, 1322, 1152; **HRMS** (ES^+) cald for $C_{19}H_{19}$ $^{35}ClO_2$: $(M+H)^+$ 314.10681. Found: 314.10598.



(E)-3-(3',4'-Dichloro-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 203

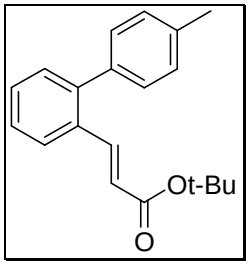
Isolated in a yield of 88% as a colourless solid. **m.p.** (DCM) 55 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69 (m, 1H, Ar*H*), 7.55 (d, 1H, CH=C*H*, J = 15.9 Hz), 7.50 (d, 1H, Ar*H*, J = 8.2 Hz), 7.44 – 7.38 (m, 3H, Ar*H*), 7.30 (m, 1H, Ar*H*), 7.14 (dd, 1H, Ar*H*, J = 2.1, 8.2 Hz), 6.34 (d, 1H, CH=C*H*, J = 15.9 Hz), 1.49 (s, 9H, C(CH_3)$_3$); **^{13}C**

NMR ($CDCl_3$, 101 MHz) δ 166.0 (quat), 141.5 (CH), 140.1 (quat), 140.0 (quat), 132.7 (quat), 132.5 (quat), 131.9 (quat), 131.4 (CH), 130.2 (2C, CH), 129.8 (CH), 129.2 (CH), 128.4 (CH), 126.8 (CH), 121.8 (CH), 80.7 (quat), 28.2 (3C, CH_3); **IR** (film/cm^{-1}) 3399, 2976, 1707, 1634, 1463, 1321, 1151; **HRMS** (ES^+) cald for $C_{19}H_{19}{}^{35}Cl_2O_2$: $(M+H)^+$ 348.06784. Found: 348.06741.



((E)-3-(3'-Bromo-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 204

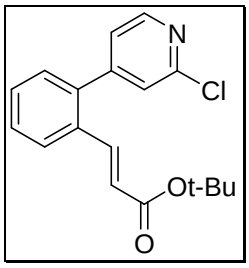
Isolated in a yield of 40% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69 (d, 1H, Ar*H*, J = 7.2 Hz), 7.58 (d, 1H, CH=C*H*, J = 16.0 Hz), 7.52 (d, 1H, Ar*H*, J = 8.0 Hz), 7.49 (s, 1H, Ar*H*), 7.44 – 7.37 (m, 2H, Ar*H*), 7.33 – 7.23 (m, 3H, Ar*H*), 6.33 (d, 1H, CH=C*H*, J = 15.6 Hz), 1.48 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.0 (quat), 142.1 (quat), 141.8 (CH), 141.2 (quat), 132.8 (quat), 132.6 (CH), 130.6 (CH), 130.3 (CH), 129.7 (CH), 128.6 (CH), 128.2 (CH), 126.7 (CH), 122.4 (quat), 121.6 (CH), 80.5 (quat), 28.2 (3C, CH_3); **IR** (film/cm^{-1}) 2978, 1708, 1632, 1367, 1321; **HRMS** (ES^+) cald for $C_{19}H_{19}{}^{79}BrO_2$: $(M+H)^+$ 358.05629. Found: 358.05770.



(E)-3-(4'-Methyl-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 205

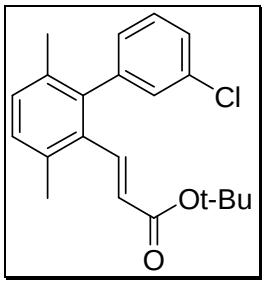
Isolated in a yield of 27% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.70 – 6.65 (m, 2H, CH=C*H*, Ar*H*), 7.43 – 7.33 (m, 3H, Ar*H*), 7.25 – 7.20 (m, 4H, Ar*H*), 6.33 (d, 1H, CH=C*H*, J = 15.6 Hz), 2.41 (s, 3H, ArCH_3), 1.48 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.3 (quat), 143.0 (quat), 142.8 (CH), 137.2 (quat), 137.1 (quat), 132.7 (quat), 130.5 (CH), 129.7 (2C, CH), 129.6 (CH), 129.0 (2C, CH),

127.4 (CH), 126.6 (CH), 120.7 (CH), 80.3 (quat), 28.2 (3C, CH_3), 21.1 (CH_3); **IR** (film/cm^{-1}) 1708, 1630, 1321, 1150; **HRMS** (ES^+) cald for $C_{20}H_{22}O_2$: $(M+H)^+$ 294.16143. Found: 294.16102.



(E)-3-[2-(2-Chloro-pyridin-4-yl)-phenyl]-acrylic acid *tert*-butyl ester 206

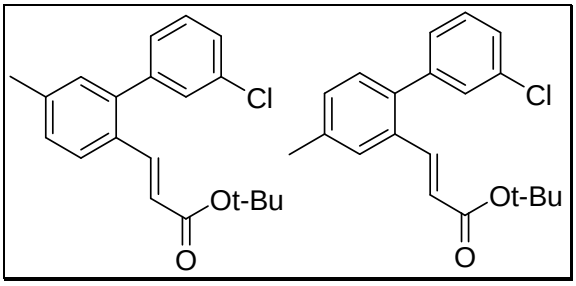
Isolated by HPLC in a yield of 19% as a colourless solid. **m.p.** (DCM) 67 – 68 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.50 (d, 1H, Ar*H*, J = 5.2 Hz), 7.72 (m, 1H, Ar*H*), 7.52 – 7.45 (m, 3H, CH=C*H*, Ar*H*), 7.36 (m, 1H, Ar*H*), 7.32 (m, 1H, Ar*H*), 7.25 (m, 1H, Ar*H*), 6.36 (d, 1H, CH=C*H*, J = 15.8 Hz), 1.50 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.7 (quat), 151.8 (quat), 151.3 (quat), 148.9 (CH), 140.5 (CH), 138.0 (quat), 132.7 (quat), 130.0 (CH), 129.8 (CH), 129.5 (CH), 127.2 (CH), 125.2 (CH), 123.7 (CH), 122.9 (CH), 81.0 (quat), 28.1 (3C, CH_3); **IR** (film/cm^{-1}) 1707, 1588, 1532, 1370, 1322, 1150.



(E)-3-(3'-Chloro-3,6-dimethyl-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 209

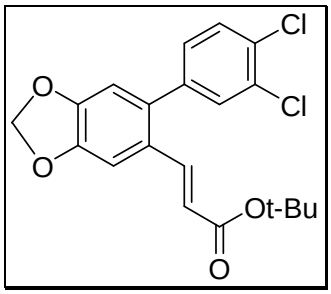
Isolated in a yield of 65% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.32 – 7.25 (m, 3H, Ar*H*, CH=C*H*), 7.14 – 7.11 (m, 3H, Ar*H*), 6.99 (m, 1H, Ar*H*), 5.67 (d, 1H, CH=C*H*, J = 16.4 Hz), 2.39 (s, 3H, ArCH_3), 2.03 (s, 3H, ArCH_3), 1.41 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 165.8 (quat), 142.4 (CH), 142.2 (quat), 140.4 (quat), 134.2 (quat), 134.1 (quat), 133.7 (quat), 133.4 (quat), 130.1 (CH), 130.0 (CH), 129.8 (CH), 129.5 (CH), 128.0 (CH), 127.1 (CH), 125.7 (CH), 80.2 (quat),

28.1 (3C, CH_3), 21.2 (CH_3), 20.5 (CH_3); **IR** (film/cm^{-1}) 2976, 1710, 1633, 1367, 1307; **HRMS** (ES^+) cald for $C_{21}H_{23}{}^{35}ClO_2$: $(M+H)^+$ 342.13811. Found: 342.13729.



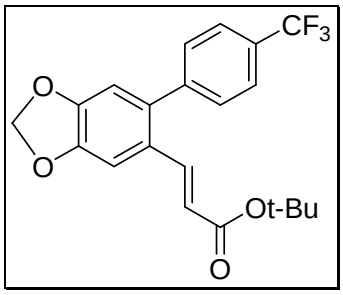
(E)-3-(3'-Chloro-4-methyl-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 210 and (E)-3-(3'-Chloro-5-methyl-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 211

Isolated as a 50:50 mixture of the title compounds in a yield of 70% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.62 – 7.51 (m, 2H, Ar*H*), 7.36 – 7.31 (m, 3H, Ar*H*), 7.26 – 7.14 (m, 3H, Ar*H*), 6.32 (d, 0.5H, CH=C*H*, J = 15.9 Hz), 6.29 (d, 0.5H, CH=C*H*, J = 15.8 Hz), 2.42 (s, 1.5H, ArCH_3), 2.40 (s, 1.5H, ArCH_3), 1.49 (s, 4.5H, C(CH_3)$_3$), 1.48 (s, 4.5H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.2 (quat), 166.1 (quat), 142.0 (CH), 142.0 (quat), 141.8 (quat), 141.8 (CH), 141.3 (quat), 140.0 (quat), 138.6 (quat), 137.9 (quat), 134.2 (2C, quat), 132.5 (quat), 130.9 (CH), 130.6 (CH), 130.2 (CH), 129.9 (quat), 129.8 (CH), 129.7 (CH), 129.4 (2C, CH), 129.0 (CH), 128.1 (CH), 128.1 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 126.6 (CH), 121.2 (CH), 120.5 (CH), 80.4 (quat), 80.3 (quat), 28.2 (3C, CH_3), 21.3 (CH_3), 21.1 (CH_3); **IR** (film/cm^{-1}) 2977, 1708, 1632, 1468, 1367, 1321, 1198; **HRMS** (ES^+) cald for $C_{20}H_{21}{}^{35}ClO_2$: $(M+H)^+$ 328.12246. Found: 328.12167.



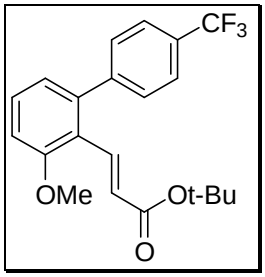
(E)-3-[6-(3,4-Dichloro-phenyl)-benzo[1,3]dioxol-5-yl]-acrylic acid *tert*-butyl ester 212

Isolated in a yield of 33% as an orange solid. **m.p.** (DCM) 135 - 136 °C. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.48 (d, 1H, Ar*H*, J = 8.2 Hz), 7.44 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.37 (d, 1H, Ar*H*, J = 2.3 Hz), 7.14 (s, 1H, Ar*H*), 7.09 (dd, 1H, Ar*H*, J = 2.1, 8.2 Hz), 6.75 (s, 1H, Ar*H*), 6.20 (d, 1H, CH=C*H*, J = 15.7 Hz), 6.04 (s, 2H, CH_2), 1.47 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 166.1 (quat), 149.1 (quat), 148.0 (quat), 141.1 (CH), 139.8 (quat), 135.6 (quat), 132.4 (quat), 131.9 (quat), 131.5 (CH), 130.1 (CH), 129.3 (CH), 126.7 (quat), 119.6 (CH), 109.9 (CH), 105.8 (CH), 101.8 (CH), 80.4 (quat), 28.2 (3C, CH_3); **IR** (film/cm^{-1}) 2976, 2925, 1703, 1630, 1616, 1471, 1230, 1150, 1039; **HRMS** (ES^+) cald for $C_{21}H_{18}$ $^{35}Cl_2O_4$: $(M+H)^+$ 392.05767. Found: 392.05867.



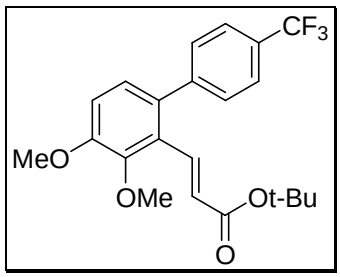
(E)-3-[6-(4-Trifluoromethyl-phenyl)-benzo[1,3]dioxol-5-yl]-acrylic acid *tert*-butyl ester 213

Isolated in a yield of 38% as a colourless solid. **m.p.** (DCM) 145 - 147 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.68 (d, 2H, Ar*H*, J = 8.1 Hz), 7.45 (d, 1H, CH=C*H*, J = 15.8 Hz), 7.39 (d, 2H, Ar*H*, J = 8.0 Hz), 7.18 (s, 1H, Ar*H*), 6.78 (s, 1H, Ar*H*), 6.21 (d, 1H, CH=C*H*, J = 15.8 Hz), 6.05 (s, 2H, CH_2), 1.46 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.2 (quat), 149.1 (quat), 148.1 (quat), 143.5 (quat), 141.3 (CH), 136.7 (quat), 130.2 (2C, CH), 129.7 (d, quat, J = 32.6 Hz), 126.7 (CH), 125.2 (q, 2C, CH, J = 3.7 Hz), 124.2 (q, CF_3, J = 272.1 Hz), 119.6 (CH), 110.1 (CH), 105.8 (CH), 101.8 (CH_2), 80.4 (quat), 28.1 (3C, CH_3); **IR** (film/cm^{-1}) 2927, 1703, 1615, 1483, 1368, 1326, 1152; **HRMS** (ES^+) cald for $C_{21}H_{19}$ F_3O_4: $(M+H)^+$ 392.12300. Found: 392.12323.



(E)-3-(6-Methoxy-4'-trifluoromethyl-biphenyl-2-yl)-acrylic acid tert-butyl ester 214

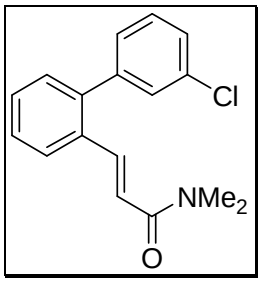
Isolated as a single regioisomer in a yield of 68% as a yellow oil. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.67 (d, 2H, Ar*H*, J = 8.0 Hz), 7.47 – 7.33 (m, 4H, CH=C*H*, Ar*H*), 6.99 (d, 1H, Ar*H*, J = 8.2 Hz), 6.90 (dd, 1H, Ar*H*, J = 7.6, 1.1 Hz), 6.55 (d, 1H, CH=C*H*, J = 16.1 Hz), 3.95 (s, 3H, OCH_3), 1.43 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 167.0 (quat), 159.3 (quat), 144.1 (quat), 143.7 (quat), 137.9 (CH), 130.2 (2C, CH), 129.9 (quat), 125.1 (q, 2C, CH, J = 3.6 Hz), 124.9 (CH), 122.6 (CH), 121.5 (quat), 110.6 (CH), 80.0 (quat), 55.7 (CH_3), 28.1 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -63.7; **IR** (film/cm^{-1}) 2976, 1702, 1624, 1467, 1325, 1257, 1151, 1123; **HRMS** (ES^+) cald for $C_{21}H_{21}F_3O_3$: $(M+H)^+$ 378.14373. Found: 378.14259.



(E)-3-(5,6-Dimethoxy-4'-trifluoromethyl-biphenyl-2-yl)-acrylic acid tert-butyl ester 215

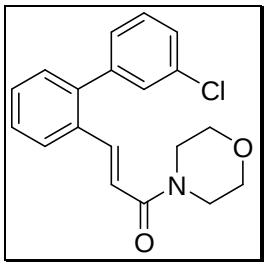
Isolated as a single isomer in a yield of 38% as a slightly yellow oil. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.65 (d, 2H, Ar*H*, J = 8.0 Hz), 7.41 (d, 1H, CH=C*H*, J = 16.2 Hz), 7.39 (d, 2H, Ar*H*, J = 7.9 Hz), 7.00 (q, 2H, Ar*H*, J = 8.5 Hz), 6.45 (d, 1H, CH=C*H*, J = 16.2 Hz), 3.94 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 1.44 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 166.6 (quat), 152.8 (quat), 148.7 (quat), 144.1 (quat), 137.9 (CH), 134.8 (quat), 130.2 (2C, CH), 129.2 (d, quat, J = 32.5 Hz), 127.0 (quat), 125.8 (CH), 125.8 (CH), 125.1 (q, 2C, CH, J = 3.6 Hz), 124.3 (q, CF_3, J

= 289.4 Hz), 112.9 (CH), 80.3 (quat), 60.2 (CH_3), 56.0 (CH_3), 28.1 (3C, CH_3); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -63.7; **IR** (film/cm^{-1}) 2937, 1706, 1479, 1325, 1153, 1125; **HRMS** (ES^+) cald for $C_{22}H_{23}F_3O_4$: $(M+H)^+$ 408.15430. Found: 408.15300.



(E)-3-(3'-Chloro-biphenyl-2-yl)-*N*,*N*-dimethyl-acrylamide 216

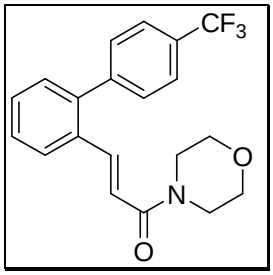
Isolated in a yield of 74% as a slightly yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.66 (m, 1H, Ar*H*), 7.59 (d, 1H, CH=C*H*, J = 15.5 Hz), 7.42 – 7.37 (m, 2H, Ar*H*), 7.35 - 7.30 (m, 4H, Ar*H*), 7.19 (m, 1H, Ar*H*), 6.74 (d, 1H, CH=C*H*, J = 15.4 Hz), 3.10 (bs, 3H, NCH_3), 3.02 (bs, 3H, NCH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5 (quat), 142.1 (quat), 141.0 (quat), 140.5 (CH), 134.2 (quat), 133.6 (quat), 130.4 (CH), 129.5 (CH), 129.1 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 127.0 (CH), 119.6 (CH), 37.4 (CH_3), 35.8 (CH_3); **IR** (film/cm^{-1}) 2927, 1650, 1609, 1393, 1140; **HRMS** (ES^+) cald for $C_{17}H_{16}{}^{35}ClNO_2$: $(M+H)^+$ 285.09149. Found: 285.09024.



(E)-3-(3'-Chloro-biphenyl-2-yl)-1-morpholin-4-yl-propenone 217

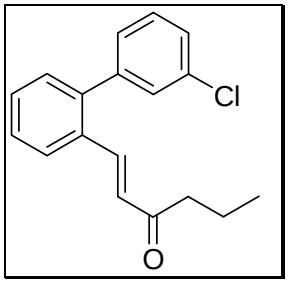
Isolated in a yield of 67% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.65 (m, 1H, Ar*H*), 7.59 (d, 1H, CH=C*H*, J = 15.6 Hz), 7.42 – 7.39 (m, 2H, Ar*H*), 7.36 – 7.35 (m, 2H, Ar*H*), 7.33 – 7.30 (m, 2H, Ar*H*), 7.20 – 7.18 (m, 1H, Ar*H*), 6.66 (d, 1H, CH=C*H*, J = 15.5 Hz), 3.69 – 3.57 (bm, 8H, CH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 165.6 (quat), 142.1 (quat), 141.3 (CH), 141.1 (quat), 134.3 (quat), 133.4 (quat), 130.5 (CH), 129.6 (CH), 129.6 (CH), 129.4 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 127.1 (CH), 118.9 (CH), 66.8 (2C, CH_2); **IR** (film/cm^{-1}) 2855, 1647, 1605, 1432,

1267, 1226, 1114; **HRMS** (ES^+) cald for $C_{19}H_{18}{}^{35}ClNO_2$: $(M+H)^+$ 327.10206. Found: 327.10100.



(E)-1-Morpholin-4-yl-3-(4'-trifluoromethyl-biphenyl-2-yl)-propenone 218

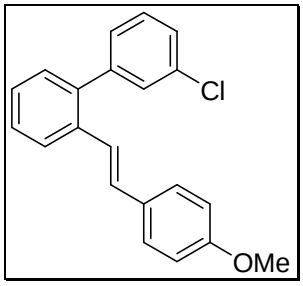
Isolated in a yield of 91% as a colourless solid. **m.p.** (DCM) 154 - 156 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.70 – 7.67 (m, 3H, Ar*H*), 7.64 (d, 1H, CH=C*H*, J = 15.6 Hz), 7.46 – 7.42 (m, 4H, Ar*H*), 7.33 (m, 1H, Ar*H*), 6.70 (d, 1H, CH=C*H*, J = 15.4 Hz), 3.69 – 3.57 (bm, 8H, CH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 165.2 (quat), 143.9 (quat), 141.4 (CH), 141.0 (quat), 133.4 (quat), 130.5 (CH), 130.0 (2C, CH), 129.6 (d, quat, J = 32.6 Hz), 129.5 (CH), 128.3 (CH), 127.1 (CH), 125.3 (q, 2C, CH, J = 7.2 Hz), 124.1 (q, CF_3, J = 272 Hz), 118.7 (CH), 66.8 (2C, CH_2), 46.2 (CH_2), 42.4 (CH_2); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ -62.7; **IR** (film/cm^{-1}) 3466, 2857, 1648, 1607, 1432, 1326, 1226, 1166, 1116, 1069; **HRMS** (ES^+) cald for $C_{20}H_{18}F_3NO_2$: $(M+H)^+$ 361.12841. Found: 361.12678.



(E)-1-(3'-Chloro-biphenyl-2-yl)-hex-1-en-3-one 219

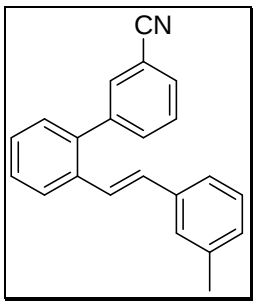
Isolated in a yield of 38% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.71 (dd, 1H, Ar*H*, J = 1.6, 7.2 Hz) 7.51 (d, 1H, CH=C*H*, J = 16.0 Hz), 7.45 – 7.34 (m, 6H, Ar*H*), 7.20 (m, 1H, Ar*H*), 6.65 (d, 1H, CH=C*H*, J = 16.4 Hz), 2.5 (t, CH_2, J = 7.4 Hz), 1.65 (sextet, CH_2, J = 7.4 Hz), 0.93 (t, 3H, CH_3, J = 7.4 Hz); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 200.6 (quat), 141.8 (quat), 141.5 (quat), 141.1 (CH), 134.4 (quat), 132.9

(quat), 130.3 (CH), 130.0 (CH), 129.8 (CH), 129.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 126.9 (CH), 42.2 (CH_2), 18.0 (CH_2), 13.8 (CH_3); **IR** (film/cm^{-1}) 2961, 1667, 1609, 1465, 1406, 1185; **HRMS** (ES^+) cald for $C_{18}H_{17}{}^{35}ClO$: $(M+H)^+$ 284.09624. Found: 284.09611.



3'-Chloro-2-[(E)-2-(4-methoxy-phenyl)-vinyl]-biphenyl 220

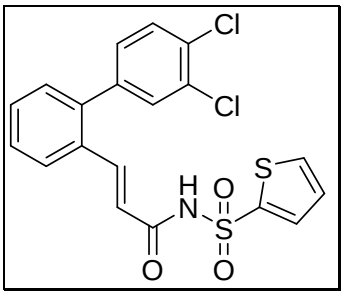
Isolated in a yield of 70% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.75 (d, 1H, Ar*H*, J = 7.6 Hz), 7.41 – 7.21 (m, 8H, Ar*H*, CH=C*H*), 7.03 (d, 2H, Ar*H*, J = 3.6 Hz), 6.97 (d, 1H, Ar*H*, J = 7.6 Hz), 6.90 (t, 1H, Ar*H*, J = 2.0 Hz), 6.79 (dd, 1H, Ar*H*, J = 1.8, 8.0 Hz), 3.80 (s, 3H, OCH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 159.9 (quat), 142.7 (quat), 139.7 (quat), 138.9 (quat), 135.4 (quat), 134.1 (quat), 130.1 (CH), 129.9 (CH), 129.8 (CH), 129.6 (CH), 129.3 (CH), 128.2 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 126.0 (CH), 119.3 (CH), 113.3 (CH), 112.0 (CH), 55.2 (CH_3); **IR** (film/cm^{-1}) 2917, 2852, 1647, 1599, 1464, 1431, 1267; **HRMS** (ES^+) cald for $C_{21}H_{17}{}^{35}ClO$: $(M+H)^+$ 320.09624. Found: 320.09655.



2'-((E)-2-m-Tolyl-vinyl)-biphenyl-3-carbonitrile 221

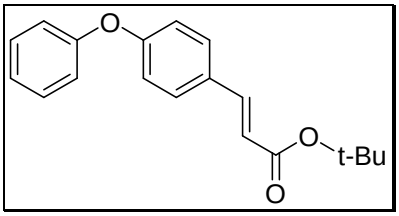
Isolated in a yield of 43% as a yellow oil. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.76 (dd, 1H, Ar*H*, J = 1.2, 7.7 Hz), 7.71 (m, 1H, Ar*H*), 7.68 (m, 1H, Ar*H*), 7.63 (td, 1H, Ar*H*, J = 1.6, 7.9 Hz), 7.4 (m, 1H, Ar*H*), 7.46 – 7.34 (m, 2H, Ar*H*), 7.28 (dd, 1H, Ar*H*, J = 1.6, 7.6 Hz), 7.22 – 7.17 (m, 3H, CH=C*H*, Ar*H*), 7.08 – 6.91 (m, 3H, CH=C*H*, Ar*H*),

2.34 (s, 3H, C*H*$_3$); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 142.3 (quat), 138.5 (quat), 138.3 (quat), 137.1 (quat), 135.6 (quat), 134.4 (CH), 133.0 (CH), 131.0 (CH), 130.8 (CH), 130.0 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 127.7 (CH), 127.4 (CH), 126.3 (CH), 126.3 (CH), 123.6 (CH), 118.7 (quat), 112.5 (quat), 21.4 (CH_3); **IR** (film/cm^{-1}) 3059, 3582, 2920, 2229, 1601, 1583, 1470, 1212; **HRMS** (EI$^+$) cald for $C_{22}H_{17}N$: $(M+H)^+$ 295.13555. Found: 295.13561.



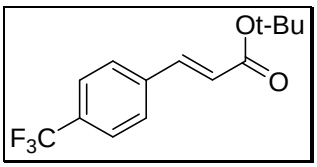
Thiophene-2-sulfonic acid [(E)-3-(3',4'-dichloro-biphenyl-2-yl)-acryloyl]-amide 238

Isolated in a yield of 68% (60% over three steps) as a colourless oil using procedure as for **158**. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.79 (bs, 1H, N*H*), 7.92 (dd, 1H, Ar*H*, J = 1.4, 3.9 Hz), 7.69 (dd, 1H, Ar*H*, J = 1.4, 5.0 Hz), 7.69 (d, 1H, CH=C*H*, J = 15.6 Hz), 7.65 (m, 1H, Ar*H*), 7.48 – 7.37 (m, 3H, Ar*H*), 7.36 (d, 1H, Ar*H*, J = 2.0 Hz), 7.30 (m, 1H, Ar*H*), 7.11 (dd, 1H, Ar*H*, J = 3.9, 5.0 Hz), 7.06 (dd, 1H, Ar*H*, J = 2.1, 8.2 Hz), 6.43 (d, 1H, CH=C*H*, J = 15.5 Hz); ^{13}C NMR ($CDCl_3$, 91 MHz) δ 162.7 (quat), 144.4 (CH), 140.9 (quat), 139.5 (quat), 138.7 (quat), 135.3 (CH), 134.2 (CH), 132.7 (quat), 132.3 (quat), 131.7 (quat), 131.2 (CH), 130.7 (CH), 130.4 (CH), 130.4 (CH), 129.2 (CH), 128.5 (CH), 127.5 (CH), 127.1 (CH), 118.7 (CH); IR (film/cm^{-1}) 3244, 1684, 1623, 1445, 1132.



(E)-3-(4'-Hydroxy-biphenyl-2-yl)-acrylic acid *tert*-butyl ester 207

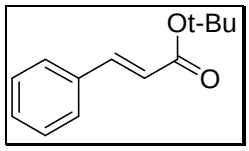
Isolated in a yield of 84% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.56 (d, 1H, CH=C*H*, J = 16.0 Hz), 7.47 (dd, 2H, Ar*H*, J = 2.0, 8.8 Hz), 7.39 – 7.35 (m, 2H, Ar*H*), 7.15 (t, 1H, Ar*H*, J = 7.4 Hz), 7.05 (d, 2H, Ar*H*, J = 8.0 Hz), 6.97 (dd, 2H, Ar*H*, J = 2.4, 8.8 Hz), 6.28 (d, 1H, CH=C*H*, J = 16.0 Hz), 1.54 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.4 (quat), 159.2 (quat), 156.3 (quat) 142.8 (CH), 129.9 (CH), 129.6 (2C, CH), 124.0 (CH), 119.6 (CH), 119.0 (CH), 118.4 (2C, CH), 80.4 (quat), 28.2 (3C, CH_3); **IR** (film/cm^{-1}) 2976, 1708, 1631, 1367, 1320.



(E)-*tert*-butyl 3-(4-(trifluoromethyl)phenyl)acrylate[202]

^{1}H NMR ($CDCl_3$, 400 MHz) δ ^{13}C NMR ($CDCl_3$, 101 MHz) δ 165.7 (quat), 141.6 (quat), 138.1 (quat, q, J = 1.5 Hz), 131.4 (CH, q, J = 32.7 Hz), 128.0 (CH), 125.8 (CH, q, J = 3.8 Hz), 123.9 (CF_3, q, J = 272.1), 122.8 (CH), 81.0 (quat), 28.1 (3C, CH_3).

The spectroscopic data was in agreement with that previously published.

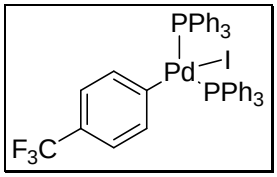


(E)-tert-butyl cinnamate

Isolated as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.58 (d, 1H, CH=C*H*, J = 15.9 Hz), 7.51 – 7.49 (m, 2 H, Ar*H*), 7.38 – 7.35 (m, 3H, Ar*H*), 6.36 (d, 1H, CH=C*H*, J = 15.9 Hz), 1.54 (s, 9H, CCH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 166.3 (quat), 143.5 (CH), 134.8 (quat), 129.9 (CH), 128.8 (2C, CH), 128.0 (2C, CH), 120.3 (CH), 80.5 (quat), 28.2 (3C, CH_3);

6.4.2 General procedure for the synthesis of aryl-palladium iodides

To a solution of tetrakis(triphenylphosphine)palladium(0) (600 mg) in DCM (15 mL) was added 1-(trifluoromethyl)-4-iodobenzene (0.1 mL) and the reaction stirred at room temperature for two hours. Solvent was removed *in vacuo* and the resulting yellow residue washed with ether then recrystallised from DCM layered with hexanes.



(4-(trifluoromethyl)phenyl)(bis(triphenylphosphine)palladium iodide 231[203]

Isolated as a yellow crystalline solid in a yield of 93%. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.54 – 7.49 (m, 12H, Ar*H*), 7.39 – 7.31 (m, 6H, Ar*H*), 7.27 – 7.23 (m, 12H, Ar*H*), 6.72 (d, 2H, Ar*H*, J = 7.6 Hz), 6.40 (d, 2H, Ar*H*, J = 8.0 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 135.7 (m, quat), 135.2 (m, quat), 134.8 (t, CH, J = 6.2 Hz), 134.5 (t, CH, J = 6.4 Hz), 131.6 (t, CH, J = 23.5 Hz), 130.0 (CH), 127.9 (t, CH, J = 5.1 Hz), 123.3 (m, quat); **^{19}F NMR** ($CDCl_3$, 235 MHz) δ – 63.3; **^{31}P NMR** ($CDCl_3$, 146 MHz) δ 23.1.

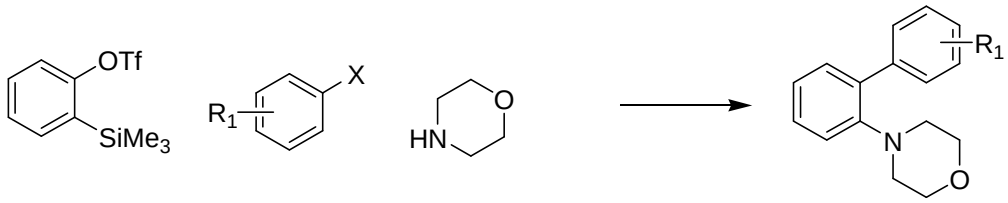
The spectroscopic data was in agreement with that previously published.

Procedure used for attempted synthesis of $[Pd[P(o\text{-}tol_3)_2]]_2$

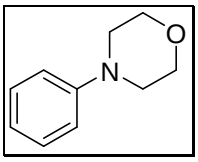
To Pd_2dba_3 (250 mg, 0.43 mmol) suspended in 30 mL of benzene was added a solution of tri-o-tolylphosphine (1.0 g, 3.4 mmol) in 30 mL of benzene. The reaction mixture was stirred at room temperature for 20 h. The brown solution was filtered and concentrated to dryness, leaving a brown oily residue. Diethyl ether (50 mL) was added and the reaction left to stand over the weekend. No precipitate was observed. Reaction was again concentrated and a sample analysed by NMR, showing several peaks by ^{31}P NMR. Further attempts to recrystallise the reaction failed.[168]

6.5 Buchwald Reactions

6.5.1 General procedure for aryl halide Buchwald reaction



To a stirred mixture of aryl iodide (1.5 equiv.), $Pd(OAc)_2$ (5 mol%), dppe (5 mol%) and CsF (3 equiv.) in DME (1 mL) was added 2-(trimethylsilyl)phenyl trifluoromethane sulfonate (**1**) (1 equiv.) and morpholine (1 equiv.). The reaction was stirred overnight at 50 ºC. After filtration through a pad of silica, the reaction was concentrated *in vacuo*. Reactions were purified by chromatography on silica gel, eluting with EtOAc/hexanes.

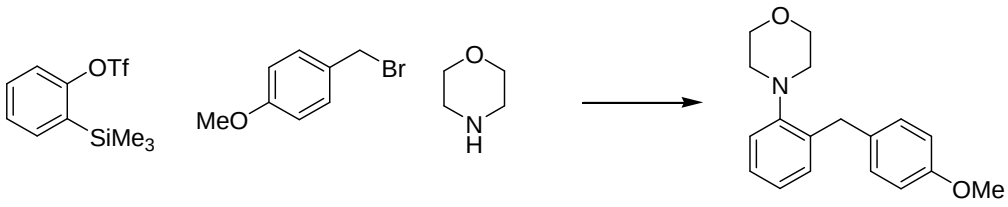


N-phenyl morpholine 242[204]

Isolated in yields of up to 98% as a slightly yellow oil. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.36 – 7.30 (m, 2H, Ar*H*), 6.99 – 6.92 (m, 3H, Ar*H*), 3.93 – 3.90 (t, 4H, CH_2, J = 4.8 Hz), 3.22 – 3.20 (t, 4H, CH_2, J = 4.8 Hz); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 151.3 (quat), 129.3 (2C, CH), 120.1 (CH), 115.8 (2C, CH), 67.0 (2C, CH_2), 49.4 (2C, CH_2).

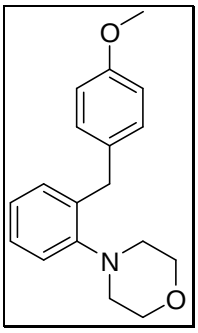
The spectroscopic data was in agreement with that previously published.

6.5.2 General procedure for the 3CC of benzyne, morpholine and 4-methoxybenzyl bromide



Morpholine (0.207 mmol, 1 equiv.) and 1-(bromomethyl)-4-methoxybenzene (0.309 mmol, 1.5 equiv.) were added to a stirred suspension of $Pd(OAc)_2$ (10.30 µmol, 5 mol%), dppe (10.30 µmol, 5 mol%) and cesium fluoride (0.618 mmol, 3 equiv.) in DME (1 ml) and under nitrogen. 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate (0.206 mmol, 1 equiv.) was added and the reaction was stirred at 50 °C overnight. The reaction was diluted with DCM, filtered through a pad of silica and concentrated. Products were purified by chromatography on silica, eluting with 10% EtOAc/Hexane.

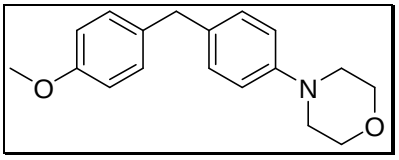
Where no palladium catalyst was used the reactions were carried out as above with the exclusion of the catalyst and ligand.



4-(2-(4-methoxybenzyl)phenyl)morpholine 241[205]

Isolated in yields of up to 12% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.22 (m, 1H, Ar*H*), 7.15 – 7.10 (m, 4H, Ar*H*), 7.05 (m, 1H, Ar*H*), 6.83 – 6.79 (m, 2H, Ar*H*), 4.03 (s, 2H, CH_2), 3.82 – 3.79 (m, 4H, CH_2), 3.78 (s, 3H, OCH_3), 2.86 – 2.84 (m, 4H, CH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 157.7 (quat), 151.2 (quat), 137.0 (quat), 133.6 (quat), 130.9 (CH), 129.8 (2C, CH), 127.1 (CH), 124.2 (CH), 120.4 (CH), 113.7 (2C, CH), 67.4 (2C, CH_2), 55.2 (CH_3), 53.0 (2C, CH_2), 35.7 (CH_2)

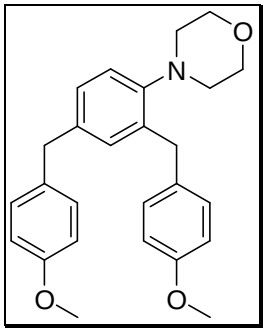
The spectroscopic data was in agreement with that previously published.



4-(4-(4-methoxybenzyl)phenyl)morpholine 243[205]

Isolated in yields of up to 34% as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.10 – 7.07 (m, 4H, Ar*H*), 6.85 – 6.81 (m, 4H, Ar*H*), 3.86 – 3.84 (m, 6H, CH_2), 3.78 (s, 3H, OCH_3), 3.13 – 3.10 (m, 4H, CH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 157.9 (quat), 149.6 (quat), 133.7 (quat), 133.3 (quat), 129.7 (2C, CH), 129.2 (2C, CH), 115.9 (2C, CH), 113.8 (2C, CH), 67.0 (2C, CH_2), 55.3 (CH_3), 49.7 (2C, CH_2), 40.1 (CH_2).

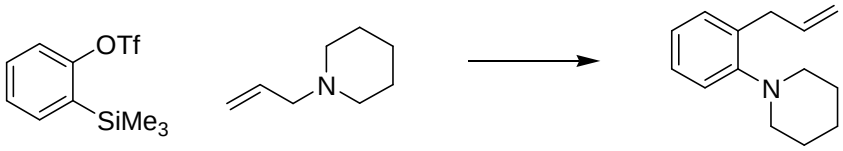
The spectroscopic data was in agreement with that previously published.



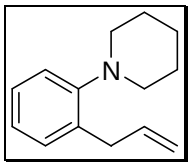
4-(2,4-bis(4-methoxybenzyl)phenyl)morpholine 244

Isolated as a colourless oil in yields of up to 16%. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.08 – 7.03 (m, 5H, Ar*H*), 7.00 – 6.97 (m, 2H, Ar*H*), 6.82 – 6.78 (m, 4H, Ar*H*), 3.98 (s, 2H, CH_2), 3.83 (s, 2H, CH_2), 3.80 – 3.76 (m, 4H, CH_2), 3.78 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.80 – 2.78 (m, 4H, CH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 157.8 (quat), 157.6 (quat), 149.3 (quat), 137.4 (quat), 136.9 (quat), 133.7 (quat), 133.3 (quat), 131.4 (CH), 129.7 (2C, CH), 129.7 (2C, CH), 127.3 (CH), 120.6 (CH), 113.7 (2C, CH), 113.6 (2C, CH), 67.4 (2C, CH_2), 55.2 (2C, CH_3), 53.1 (2C, CH_2), 40.4 (CH_2), 35.8 (CH_2).

6.5.3 General procedure for the benzyne aza-Claisen reaction

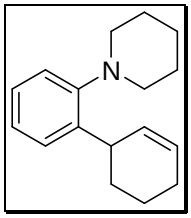


To a suspension of CsF (0.9 mmol, 3 equiv.) in toluene/MeCN (3:1, 1.5 mL) was added allylpiperidine (0.45 mmol, 1.5 euiqv.) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.3 mmol, 1 equiv.). The reaction was sealed and heated to 110 ºC for 48 hours. After diluting with DCM, the reaction was filtered and concentrated then purified by chromatography on silica gel, eluting with 3:1 heaxane/DCM.



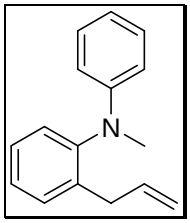
1-(2-allylphenyl)piperidine 250

Isolated in a yield of 92% as a light yellow oil. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.23 – 7.17 (m, 2H, Ar*H*), 7.08 (dd, 1H, Ar*H*, J = 1.2, 7.9), 7.03 (dt, 1H, Ar*H*, J = 1.4, 7.4 Hz), 6.01 (tdd, 1H, CH_2=C*H*, J = 6.6, 10.0, 16.7 Hz), 5.16 – 5.07 (m, 2H, CH=CH_2), 3.49 (d, 2H, CH_2, J = 6.6 Hz), 2.85 – 2.82 (m, 4H, CH_2), 1.75 – 1.69 (m, 4H, CH_2), 1.61 – 1.54 (m, 2H, CH_2); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 152.7 (quat), 138.0 (quat), 134.9 (CH), 129.8 (CH), 126.7 (CH), 123.1 (CH), 119.7 (CH), 115.4 (CH_2), 54.0 (2C, CH_2), 34.8 (CH_2), 26.5 (CH_2), 24.3 (CH_2); **IR** (film/cm^{-1}) 2933, 2853, 2800, 1489, 1450, 1226; **HRMS** (EI^+) cald for $C_{14}H_{19}N$: $(M+H)^+$ 201.15120. Found: 201.15100



1-(2-(cyclohex-2-enyl)phenyl)piperidine 252

Isolated in a yield of 71% as a light yellow oil. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.27 – 7.07 (m, 4H, Ar*H*), 5.90 (m, 1H, CH=C*H*), 5.66 (m, 1H, CH=C*H*), 4.03 (m, 1H, C*H*), 2.92 – 2.78 (m, 4H, CH_2), 2.18 – 2.11 (m, 2H, CH_2), 2.05 (m, 1H, CH_2), 1.83 (m, 1H, CH_2), 1.78 – 1.66 (m, 5H, CH_2), 1.60 – 1.48 (m, 3H, CH_2); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 152.5 (quat), 142.3 (quat), 131.5 (CH), 128.4 (CH), 127.5 (CH), 126.4 (CH), 123.7 (CH), 120.4 (CH), 54.8 (CH_2), 35.4 (CH), 31.8 (CH_2), 26.7 (CH_2), 25.0 (CH_2), 24.2 (CH_2), 21.9 (CH_2); **IR** (film/cm^{-1}) 3018, 2931, 2854, 2790, 1487, 1449, 1224; **HRMS** (EI^+) cald for $C_{17}H_{23}N$: $(M+H)^+$ 241.18250. Found: 241.18250.



N-(2-allylphenyl)-N-methylbenzenamine 253[206]

Isolated in a yield of 91% as a slightly yellow oil. **^{1}H NMR** ($CDCl_3$, 360 MHz) δ 7.45 – 7.21 (m, 6H, Ar*H*), 6.82 (t, 1H, Ar*H*), 6.66 – 6.63 (m, 2H, Ar*H*), 6.00 (tdd,1H, C*H*=CH_2, J = 6.7, 10.2, 16.9 Hz,), 5.16 – 5.09 (m, 2H, CH=CH_2), 3.39 (d, 2H, CH_2, J = 6.7 Hz), 3.32 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 91 MHz) δ 149.3 (quat), 146.6 (quat), 138.9 (quat), 136.9 (CH), 130.5 (CH), 128.8 (2C, CH), 128.6 (CH), 128.0 (CH), 126.6 (CH), 116.8 (CH), 115.8 (CH_2), 112.9 (2C, CH), 39.6 (CH_3), 35.4 (CH_2).

The spectroscopic data was in agreement with that previously published.

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